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(54) **Compositions and methods for the diagnosis and treatment of tumor**

(57) The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

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DescriptionFIELD OF THE INVENTION

[0001] The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

BACKGROUND OF THE INVENTION

[0002] Malignant tumors (cancers) are the second leading cause of death in the United States, after heart disease (Boring et al., CA Cancer J. Clin. 43:7 (1993)). Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites via a process called metastasis. In a cancerous state, a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

[0003] In attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify transmembrane or otherwise membrane-associated polypeptides that are specifically expressed on the surface of one or more particular type(s) of cancer cell as compared to on one or more normal non-cancerous cell(s). Often, such membrane-associated polypeptides are more abundantly expressed on the surface of the cancer cells as compared to on the surface of the non-cancerous cells. The identification of such tumor-associated cell surface antigen polypeptides has given rise to the ability to specifically target cancer cells for destruction via antibody-based therapies. In this regard, it is noted that antibody-based therapy has proved very effective in the treatment of certain cancers. For example, HERCEPTIN® and RITUXAN® (both from Genentech Inc., South San Francisco, California) are antibodies that have been used successfully to treat breast cancer and non-Hodgkin's lymphoma, respectively. More specifically, HERCEPTIN® is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) proto-oncogene. HER2 protein overexpression is observed in 25-30% of primary breast cancers. RITUXAN® is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Both these antibodies are recombinantly produced in CHO cells.

[0004] In other attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify (1) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (2) polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (3) polypeptides whose expression is specifically limited to only a single (or very limited number of different) tissue type(s) in both the cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue). Such polypeptides may remain intracellularly located or may be secreted by the cancer cell. Moreover, such polypeptides may be expressed not by the cancer cell itself, but rather by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Such secreted polypeptides are often proteins that provide cancer cells with a growth advantage over normal cells and include such things as, for example, angiogenic factors, cellular adhesion factors, growth factors, and the like. Identification of antagonists of such non-membrane associated polypeptides would be expected to serve as effective therapeutic agents for the treatment of such cancers. Furthermore, identification of the expression pattern of such polypeptides would be useful for the diagnosis of particular cancers in mammals.

[0005] Despite the above identified advances in mammalian cancer therapy, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of tumor in a mammal and for effectively inhibiting neoplastic cell growth, respectively. Accordingly, it is an objective of the present invention to identify: (1) cell membrane-associated polypeptides that are more abundantly expressed on one or more type(s) of cancer cell(s) as compared to on normal cells or on other different cancer cells, (2) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) (or by other cells that produce polypeptides having a potentiating effect on the growth of cancer cells) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (3) non-membrane-associated polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (4) polypeptides whose expression is specifically limited to only a single (or very limited number of different) tissue type(s) in both a cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue), and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals. It is also an objective of the present invention to identify cell membrane-associated, secreted or intracellular polypeptides whose expression is limited to a single or very limited number of tissues, and to use those polypeptides, and their encoding

nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals.

SUMMARY OF THE INVENTION

A. Embodiments

[0006] In the present specification, Applicants describe for the first time the identification of various cellular polypeptides (and their encoding nucleic acids or fragments thereof) which are expressed to a greater degree on the surface of or by one or more types of cancer cell(s) as compared to on the surface of or by one or more types of normal non-cancer cells. Alternatively, such polypeptides are expressed by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Again alternatively, such polypeptides may not be overexpressed by tumor cells as compared to normal cells of the same tissue type, but rather may be specifically expressed by both tumor cells and normal cells of only a single or very limited number of tissue types (preferably tissues which are not essential for life, e.g., prostate, etc.). All of the above polypeptides are herein referred to as Tumor-associated Antigenic Target polypeptides ("TAT" polypeptides) and are expected to serve as effective targets for cancer therapy and diagnosis in mammals.

[0007] Accordingly, in one embodiment of the present invention, the invention provides an isolated nucleic acid molecule having a nucleotide sequence that encodes a tumor-associated antigenic target polypeptide or fragment thereof (a "TAT" polypeptide).

[0008] In certain aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80 % nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule encoding a full-length TAT polypeptide having an amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

[0009] In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80 % nucleic acid sequence identity, alternatively at least about 81% , 82 % , 83% , 84% , 85% , 86 % , 87% , 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule comprising the coding sequence of a full-length TAT polypeptide cDNA as disclosed herein, the coding sequence of a TAT polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length. TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

[0010] In further aspects, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80 % nucleic acid sequence identity, alternatively at least about 81 % , 82 % , 83 % , 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule that encodes the same mature polypeptide encoded by the full-length coding region of any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

[0011] Another aspect of the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide (s) are disclosed herein. Therefore, soluble extracellular domains of the herein described TAT polypeptides are contemplated.

[0012] In other aspects, the present invention is directed to isolated nucleic acid molecules which hybridize to (a) a nucleotide sequence encoding a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the nucleotide sequence of (a). In this regard, an embodiment of the present invention is directed to fragments of a full-length TAT polypeptide coding sequence, or the complement thereof, as disclosed herein, that may find use as, for example, hybridization probes useful as, for example, diagnostic probes, antisense oligonucleotide probes, or for encoding fragments of a full-length TAT polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-TAT polypeptide antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide. Such nucleic acid fragments are usually at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210,

220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a TAT polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the TAT polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which TAT polypeptide-encoding nucleotide sequence fragment (s) are novel. All of such novel fragments of TAT polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the TAT polypeptide fragments encoded by these nucleotide molecule fragments, preferably those TAT polypeptide fragments that comprise a binding site for an anti-TAT antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide.

[0013] In another embodiment, the invention provides isolated TAT polypeptides encoded by any of the isolated nucleic acid sequences hereinabove identified.

[0014] In a certain aspect, the invention concerns an isolated TAT polypeptide, comprising an amino acid sequence having at least about 80 % amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity, to a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide protein, with or without the signal peptide, as disclosed herein, an amino acid sequence encoded by any of the nucleic acid sequences disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein.

[0015] In a further aspect, the invention concerns an isolated TAT polypeptide comprising an amino acid sequence having at least about 80 % amino acid sequence identity, alternatively at least about 81 % , 82 % , 83 % , 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91 % , 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

[0016] In a specific aspect, the invention provides an isolated TAT polypeptide without the N-terminal signal sequence and/or without the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

[0017] Another aspect of the invention provides an isolated TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

[0018] In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

[0019] In other embodiments, the invention provides isolated chimeric polypeptides comprising any of the herein described TAT polypeptides fused to a heterologous (non-TAT) polypeptide. Example of such chimeric molecules comprise any of the herein described TAT polypeptides fused to a heterologous polypeptide such as, for example, an epitope tag sequence or a Fc region of an immunoglobulin.

[0020] In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, single-chain antibody or antibody that competitively inhibits the binding of an anti-TAT polypeptide antibody to its respective antigenic epitope. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the antibodies of the present invention may be detectably labeled, attached to a solid support, or the like.

[0021] In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described antibodies. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described antibodies is further provided and comprises culturing host cells under conditions suitable for expression of the desired antibody and

recovering the desired antibody from the cell culture.

[0022] In another embodiment, the invention provides oligopeptides ("TAT binding oligopeptides") which bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding oligopeptides of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding oligopeptides of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding oligopeptides of the present invention may be detectably labeled, attached to a solid support, or the like.

[0023] In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described TAT binding oligopeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described TAT binding oligopeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired oligopeptide and recovering the desired oligopeptide from the cell culture.

[0024] In another embodiment, the invention provides small organic molecules ("TAT binding organic molecules") which bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding organic molecules of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding organic molecules of the present invention preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding organic molecules of the present invention may be detectably labeled, attached to a solid support, or the like.

[0025] In a still further embodiment, the invention concerns a composition of matter comprising a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

[0026] In yet another embodiment, the invention concerns an article of manufacture comprising a container and a composition of matter contained within the container, wherein the composition of matter may comprise a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein. The article may further optionally comprise a label affixed to the container, or a package insert included with the container, that refers to the use of the composition of matter for the therapeutic treatment or diagnostic detection of a tumor.

[0027] Another embodiment of the present invention is directed to the use of a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT polypeptide antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, for the preparation of a medicament useful in the treatment of a condition which is responsive to the TAT polypeptide, chimeric TAT polypeptide, anti-TAT polypeptide antibody, TAT binding oligopeptide, or TAT binding organic molecule.

B. Additional Embodiments

[0028] Another embodiment of the present invention is directed to a method for inhibiting the growth of a cell that expresses a TAT polypeptide, wherein the method comprises contacting the cell with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, and wherein the binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes inhibition of the growth of the cell expressing the TAT polypeptide. In preferred embodiments, the cell is a cancer cell and binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes death of the cell expressing the TAT polypeptide. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

[0029] Yet another embodiment of the present invention is directed to a method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed, in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

[0030] Yet another embodiment of the present invention is directed to a method of determining the presence of a TAT polypeptide in a sample suspected of containing the TAT polypeptide, wherein the method comprises exposing the sample to an antibody, oligopeptide or small organic molecule that binds to the TAT polypeptide and determining binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide in the sample, wherein the presence of such binding is indicative of the presence of the TAT polypeptide in the sample. Optionally, the sample may contain cells (which may be cancer cells) suspected of expressing the TAT polypeptide. The antibody, TAT binding oligopeptide or TAT binding organic molecule employed in the method may optionally be detectably labeled, attached to a solid support, or the like.

[0031] A further embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises detecting the level of expression of a gene encoding a TAT polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal non-cancerous cells of the same tissue origin or type, wherein a higher level of expression of the TAT polypeptide in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

[0032] Another embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises (a) contacting a test sample comprising tissue cells obtained from the mammal with an antibody, oligopeptide or small organic molecule that binds to a TAT polypeptide and (b) detecting the formation of a complex between the antibody, oligopeptide or small organic molecule and the TAT polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in the mammal. Optionally, the antibody, TAT binding oligopeptide or TAT binding organic molecule employed is detectably labeled, attached to a solid support, or the like, and/or the test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

[0033] Yet another embodiment of the present invention is directed to a method for treating or preventing a cell proliferative disorder associated with altered, preferably increased, expression or activity of a TAT polypeptide, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a TAT polypeptide. Preferably, the cell proliferative disorder is cancer and the antagonist of the TAT polypeptide is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide. Effective treatment or prevention of the cell proliferative disorder may be a result of direct killing or growth inhibition of cells that express a TAT polypeptide or by antagonizing the cell growth potentiating activity of a TAT polypeptide.

[0034] Yet another embodiment of the present invention is directed to a method of binding an antibody, oligopeptide or small organic molecule to a cell that expresses a TAT polypeptide, wherein the method comprises contacting a cell that expresses a TAT polypeptide with said antibody, oligopeptide or small organic molecule under conditions which are suitable for binding of the antibody, oligopeptide or small organic molecule to said TAT polypeptide and allowing binding therebetween.

[0035] Other embodiments of the present invention are directed to the use of (a) a TAT polypeptide, (b) a nucleic acid encoding a TAT polypeptide or a vector or host cell comprising that nucleic acid, (c) an anti-TAT polypeptide antibody, (d) a TAT-binding oligopeptide, or (e) a TAT-binding small organic molecule in the preparation of a medicament useful for (i) the therapeutic treatment or diagnostic detection of a cancer or tumor, or (ii) the therapeutic treatment or prevention of a cell proliferative disorder.

[0036] Another embodiment of the present invention is directed to a method for inhibiting the growth of a cancer cell, wherein the growth of said cancer cell is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide (wherein the TAT polypeptide may be expressed either by the cancer cell itself or a cell that produces polypeptide(s) that have a growth potentiating effect on cancer cells), wherein the method comprises contacting the TAT polypeptide with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth-potentiating activity of the TAT polypeptide and, in turn, inhibiting the growth of the cancer cell. Preferably the growth of the cancer cell is completely inhibited. Even more preferably, binding of the antibody, oligopeptide or small organic molecule to the TAT polypeptide induces the death of the cancer cell. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

[0037] Yet another embodiment of the present invention is directed to a method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth potentiating activity of said TAT polypeptide and resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain

antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

C. Further Additional Embodiments

[0038] In yet further embodiments, the invention is directed to the following set of potential claims for this application:

1. Isolated nucleic acid having a nucleotide sequence that has at least 80 % nucleic acid sequence identity to:

- (a) a DNA molecule encoding the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) a DNA molecule encoding the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) a DNA molecule encoding an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide;
- (d) a DNA molecule encoding an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide;
- (e) the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29);
- (f) the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
- (g) the complement of (a), (b), (c), (d), (e) or (f).

2. Isolated nucleic acid having;

- (a) a nucleotide sequence that encodes the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) a nucleotide sequence that encodes the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29);
- (f) the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (g) the complement of (a), (b), (c), (d), (e) or (f).

3. Isolated nucleic acid that hybridizes to:

- (a) a nucleic acid that encodes the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) a nucleic acid that encodes the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) a nucleic acid that encodes an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide;
- (d) a nucleic acid that encodes an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide;
- (e) the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29);
- (f) the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
- (g) the complement of (a), (b), (c), (d), (e) or (f).

4. The nucleic acid of Claim 3, wherein the hybridization occurs under stringent conditions.

5. The nucleic acid of Claim 3 which is at least about 5 nucleotides in length.

6. An expression vector comprising the nucleic acid of Claim 1, 2 or 3.

7. The expression vector of Claim 6, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

8. A host cell comprising the expression vector of Claim 7.

9. The host cell of Claim 8 which is a CHO cell, an *E. coli* cell or a yeast cell.

10. A process for producing a polypeptide comprising culturing the host cell of Claim 8 under conditions suitable for expression of said polypeptide and recovering said polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NOS: 29).

12. An isolated polypeptide having:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

13. A chimeric polypeptide comprising the polypeptide of Claim 11 or 12 fused to a heterologous polypeptide.

14. The chimeric polypeptide of Claim 13, wherein said heterologous polypeptide is an epitope tag sequence or an Fc region of an immunoglobulin.

15. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

16. An isolated antibody that binds to a polypeptide having:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO: 107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

17. The antibody of Claim 15 or 16 which is a monoclonal antibody.

18. The antibody of Claim 15 or 16 which is an antibody fragment.

19. The antibody of Claim 15 or 16 which is a chimeric or a humanized antibody.

20. The antibody of Claim 15 or 16 which is conjugated to a growth inhibitory agent.

21. The antibody of Claim 15 or 16 which is conjugated to a cytotoxic agent.

22. The antibody of Claim 21, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
23. The antibody of Claim 21, wherein the cytotoxic agent is a toxin.
24. The antibody of Claim 23, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
25. The antibody of Claim 23, wherein the toxin is a maytansinoid.
26. The antibody of Claim 15 or 16 which is produced in bacteria.
27. The antibody of Claim 15 or 16 which is produced in CHO cells.
28. The antibody of Claim 15 or 16 which induces death of a cell to which it binds.
29. The antibody of Claim 15 or 16 which is detectably labeled.
30. An isolated nucleic acid having a nucleotide sequence that encodes the antibody of Claim 15 or 16.
31. An expression vector comprising the nucleic acid of Claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.
32. A host cell comprising the expression vector of Claim 31.
33. The host cell of Claim 32 which is a CHO cell, an *E. coli* cell or a yeast cell.
34. A process for producing an antibody comprising culturing the host cell of Claim 32 under conditions suitable for expression of said antibody and recovering said antibody from the cell culture.
35. An isolated oligopeptide that binds to a polypeptide having at least 80% amino acid sequence identity to:
 - (a) the polypeptide shown in Figure 107 (SEQ ID NOS:107)
 - (b) the polypeptide shown in Figure 107 (SEQ ID NO:107) lacking its associated signal peptide;
 - (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
 - (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
 - (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
 - (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).
36. An isolated oligopeptide that binds to a polypeptide having:
 - (a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
 - (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
 - (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
 - (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
 - (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
 - (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).
37. The oligopeptide of Claim 35 or 36 which is conjugated to a growth inhibitory agent.
38. The oligopeptide of Claim 35 or 36 which is conjugated to a cytotoxic agent.
39. The oligopeptide of Claim 38, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
40. The oligopeptide of Claim 38, wherein the cytotoxic agent is a toxin.
41. The oligopeptide of Claim 40, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
42. The oligopeptide of Claim 40, wherein the toxin is a maytansinoid.
43. The oligopeptide of Claim 35 or 36 which induces death of a cell to which it binds.
44. The oligopeptide of Claim 35 or 36 which is detectably labeled.
45. A TAT binding organic molecule that binds to a polypeptide having at least 80% amino acid sequence identity to:
 - (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
 - (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
 - (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;

- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

46. The organic molecule of Claim 45 that binds to a polypeptide having:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

47. The organic molecule of Claim 45 or 46 which is conjugated to a growth inhibitory agent.

48. The organic molecule of Claim 45 or 46 which is conjugated to a cytotoxic agent.

49. The organic molecule of Claim 48, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

50. The organic molecule of Claim 48, wherein the cytotoxic agent is a toxin.

51. The organic molecule of Claim 50, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

52. The organic molecule of Claim 50, wherein the toxin is a maytansinoid.

53. The organic molecule of Claim 45 or 46 which induces death of a cell to which it binds.

54. The organic molecule of Claim 45 or 46 which is detectably labeled.

55. A composition of matter comprising:

- (a) the polypeptide of Claim 11;
- (b) the polypeptide of Claim 12;
- (c) the chimeric polypeptide of Claim 13;
- (d) the antibody of Claim 15;
- (e) the antibody of Claim 16;
- (f) the oligopeptide of Claim 35;
- (g) the oligopeptide of Claim 36;
- (h) the TAT binding organic molecule of Claim 45; or
- (i) the TAT binding organic molecule of Claim 46; in combination with a carrier.

56. The composition of matter of Claim 55, wherein said carrier is a pharmaceutically acceptable carrier.

57. An article of manufacture comprising:

- (a) a container; and
- (b) the composition of matter of Claim 55 contained within said container.

58. The article of manufacture of Claim 57 further comprising a label affixed to said container, or a package insert included with said container, referring to the use of said composition of matter for the therapeutic treatment of or the diagnostic detection of a cancer.

59. A method of inhibiting the growth of a cell that expresses a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated

signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein, the binding of said antibody, oligopeptide or organic molecule to said protein thereby causing an inhibition of growth of said cell.

60. The method of Claim 59, wherein said antibody is a monoclonal antibody.

61. The method of Claim 59, wherein said antibody is an antibody fragment.

62. The method of Claim 59, wherein said antibody is a chimeric or a humanized antibody.

63. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

64. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

65. The method of Claim 64, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

66. The method of Claim 64, wherein the cytotoxic agent is a toxin.

67. The method of Claim 66, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

68. The method of Claim 66, wherein the toxin is a maytansinoid.

69. The method of Claim 59, wherein said antibody is produced in bacteria.

70. The method of Claim 59, wherein said antibody is produced in CHO cells.

71. The method of Claim 59, wherein said cell is a cancer cell.

72. The method of Claim 71, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

73. The method of Claim 71, wherein said cancer cell is selected from the group consisting of a lung cancer cell and an ovarian cancer cell.

74. The method of Claim 71, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

75. The method of Claim 59 which causes the death of said cell.

76. The method of Claim 59, wherein said protein has:

(a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);

(b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29).

77. A method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in Figure 107 (SEQ ID NO:107);

(b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29), said method comprising administering to said mammal a therapeutically effective amount of an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said mammal.

78. The method of Claim 77, wherein said antibody is a monoclonal antibody.

79. The method of Claim 77, wherein said antibody is an antibody fragment.
 80. The method of Claim 77, wherein said antibody is a chimeric or a humanized antibody.
 81. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.
 82. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.
 83. The method of Claim 82, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
 84. The method of Claim 82, wherein the cytotoxic agent is a toxin.
 85. The method of Claim 84, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
 86. The method of Claim 84, wherein the toxin is a maytansinoid.
 87. The method of Claim 77, wherein said antibody is produced in bacteria.
 88. The method of Claim 77, wherein said antibody is produced in CHO cells.
 89. The method of Claim 77, wherein said tumor is further exposed to radiation treatment or a chemotherapeutic agent.
 90. The method of Claim 77, wherein said tumor is a lung tumor or an ovarian tumor.
 91. The method of Claim 77, wherein said protein is more abundantly expressed by the cancerous cells of said tumor as compared to a normal cell of the same tissue origin.
 92. The method of Claim 77, wherein said protein has:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO: 107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

93. A method of determining the presence of a protein in a sample suspected of containing said protein, wherein said protein has at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO: 107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29), said method comprising exposing said sample to an antibody, oligopeptide or organic molecule that binds to said protein and determining binding of said antibody, oligopeptide or organic molecule to said protein in said sample, wherein binding of the antibody, oligopeptide or organic molecule to said protein is indicative of the presence of said protein in said sample.

94. The method of Claim 93, wherein said sample comprises a cell suspected of expressing said protein.
 95. The method of Claim 94, wherein said cell is a cancer cell.
 96. The method of Claim 93, wherein said antibody, oligopeptide or organic molecule is detectably labeled.
 97. The method of Claim 93, wherein said protein has:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO: 107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;

107), lacking its associated signal peptide sequence;
 (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in
 Figures 29 (SEQ ID NO:29).

98. A method of diagnosing the presence of a tumor in a mammal, said method comprising determining the level
 of expression of a gene encoding a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
 (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
 (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal
 peptide;
 (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated
 signal peptide;
 (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ
 ID NO: 29), in a test sample of tissue cells obtained from said mammal and in a control sample of known normal
 cells of the same tissue origin, wherein a higher level of expression of said protein in the test sample, as
 compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample
 was obtained.

99. The method of Claim 98, wherein the step of determining the level of expression of a gene encoding said protein
 comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.

100. The method of Claim 98, wherein the step determining the level of expression of a gene encoding said protein
 comprises employing an antibody in an immunohistochemistry or Western blot analysis.

101. The method of Claim 98, wherein said protein has:

(a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
 (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide
 sequence;
 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:
 107), with its associated signal peptide sequence;
 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:
 107), lacking its associated signal peptide sequence;
 (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure
 29 (SEQ ID NO: 29).

102. A method of diagnosing the presence of a tumor in a mammal, said method comprising contacting a test sample
 of tissue cells obtained from said mammal with an antibody, oligopeptide or organic molecule that binds to a protein
 having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
 (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
 (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal
 peptide;
 (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated
 signal peptide;
 (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ
 ID NO:29), and detecting the formation of a complex between said antibody, oligopeptide or organic molecule
 and said protein in the test sample, wherein the formation of a complex is indicative of the presence of a tumor
 in said mammal.

103. The method of Claim 102, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

104. The method of Claim 102, wherein said test sample of tissue cells is obtained from an individual suspected of
 having a cancerous tumor.

105. The method of Claim 102, wherein said protein has:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

106. A method for treating or preventing a cell proliferative disorder associated with increased expression or activity of a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal-peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO:29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29), said method comprising administering to a subject in need of such treatment an effective amount of an antagonist of said protein, thereby effectively treating or preventing said cell proliferative disorder.

107. The method of Claim 106, wherein said cell proliferative disorder is cancer.

108. The method of Claim 106, wherein said antagonist is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide.

109. A method of binding an antibody, oligopeptide or organic molecule to a cell that expresses a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein and allowing the binding of the antibody, oligopeptide or organic molecule to said protein to occur, thereby binding said antibody, oligopeptide or organic molecule to said cell.

110. The method of Claim 109, wherein said antibody is a monoclonal antibody.

111. The method of Claim 109, wherein said antibody is an antibody fragment.

112. The method of Claim 109, wherein said antibody is a chimeric or a humanized antibody.

113. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

114. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

115. The method of Claim 114, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

116. The method of Claim 114, wherein the cytotoxic agent is a toxin.

117. The method of Claim 116, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

118. The method of Claim 116, wherein the toxin is a maytansinoid.

119. The method of Claim 109, wherein said antibody is produced in bacteria.

120. The method of Claim 109, wherein said antibody is produced in CHO cells.

121. The method of Claim 109, wherein said cell is a cancer cell.

122. The method of Claim 121, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

123. The method of Claim 121, wherein said cancer cell is a lung cancer cell and an ovarian cancer cell.

124. The method of Claim 123, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

125. The method of Claim 109 which causes the death of said cell.

126. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

127. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treating a tumor.

128. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

129. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

130. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of medicament for treating a tumor.

131. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

132. Use of a host cell as claimed in any of Claims 8, 9, 32, or 33 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

133. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treating a tumor.

134. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

135. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

136. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treating a tumor.

137. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

138. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

139. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treating a tumor.

140. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

141. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

142. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treating a tumor.

143. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

144. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

145. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treating a tumor.

146. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

147. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

148. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treating a tumor.

149. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

150. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

151. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treating a tumor.

152. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

153. A method for inhibiting the growth of a cell, wherein the growth of said cell is at least in part dependent upon

a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO:29), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby inhibiting the growth of said cell.

154. The method of Claim 153, wherein said cell is a cancer cell.

155. The method of Claim 153, wherein said protein is expressed by said cell.

156. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

157. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein induces the death of said cell.

158. The method of Claim 153, wherein said antibody is a monoclonal antibody.

159. The method of Claim 153, wherein said antibody is an antibody fragment.

160. The method of Claim 153, wherein said antibody is a chimeric or a humanized antibody.

161. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

162. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

163. The method of Claim 162, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

164. The method of Claim 162, wherein the cytotoxic agent is a toxin.

165. The method of Claim 164, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

166. The method of Claim 164, wherein the toxin is a maytansinoid.

167. The method of Claim 153, wherein said antibody is produced in bacteria.

168. The method of Claim 153, wherein said antibody is produced in CHO cells.

169. The method of Claim 153, wherein said protein has:

- (a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);
- (b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in Figures 29 (SEQ ID NO: 29); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

170. A method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in Figure 107 (SEQ ID NO:107);
- (b) the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ

ID NO:29), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said tumor.

171. The method of Claim 170, wherein said protein is expressed by cells of said tumor.

172. The method of Claim 170, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

173. The method of Claim 170, wherein said antibody is a monoclonal antibody.

174. The method of Claim 170, wherein said antibody is an antibody fragment.

175. The method of Claim 170, wherein said antibody is a chimeric or a humanized antibody.

176. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

177. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

178. The method of Claim 177, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

179. The method of Claim 177, wherein the cytotoxic agent is a toxin.

180. The method of Claim 179, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

181. The method of Claim 179, wherein the toxin is a maytansinoid.

182. The method of Claim 170, wherein said antibody is produced in bacteria.

183. The method of Claim 170, wherein said antibody is produced in CHO cells.

184. The method of Claim 170, wherein said protein has:

(a) the amino acid sequence shown in Figure 107 (SEQ ID NO:107);

(b) the amino acid sequence shown in Figure 107 (SEQ ID NO:107), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 107 (SEQ ID NO: 107), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in Figure 29 (SEQ ID NO: 29).

Yet further embodiments of the present invention will be evident to the skilled artisan upon a reading of the present specification.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039]

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a TAT21 1 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA219894".

Figure 107 shows the amino acid sequence (SEQ ID NO:107) derived from the coding sequence of SEQ ID NO: 29 shown in Figure 29.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

[0040] The terms "TAT polypeptide" and "TAT" as used herein and when immediately followed by a numerical designation, refer to various polypeptides, wherein the complete designation (i.e., TAT/number) refers to specific polypeptide sequences as described herein. The terms "TAT/number polypeptide" and "TAT/number" wherein the term "number" is provided as an actual numerical designation as used herein e.g TAT211 encompass native sequence polypeptides, polypeptide variants and fragments of native sequence polypeptides and polypeptide variants (which are further defined herein). The TAT polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "TAT polypeptide" refers to each individual TAT/number polypeptide disclosed herein. All disclosures in this specification which refer to the "TAT

polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, formation of TAT binding oligopeptides to or against, formation of TAT binding organic molecules to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "TAT polypeptide" also includes

variants of the TAT/number polypeptides disclosed herein.

[0041] A "native sequence TAT polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding TAT polypeptide derived from nature. Such native sequence TAT polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence TAT polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific TAT polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In certain embodiments of the invention, the native sequence TAT polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons (if indicated) are shown in bold font and underlined in the figures. Nucleic acid residues indicated as "N" in the accompanying figures are any nucleic acid residue. However, while the TAT polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the TAT polypeptides.

[0042] The TAT polypeptide "extracellular domain" or "ECD" refers to a form of the TAT polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a TAT polypeptide ECD will have less than 1 % of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the TAT polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a TAT polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

[0043] The approximate location of the "signal peptides" of the various TAT polypeptides disclosed herein may be shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

[0044] "TAT polypeptide variant" means a TAT polypeptide, preferably an active TAT polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Such TAT polypeptide variants include, for instance, TAT polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a TAT polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide sequence as disclosed herein. Ordinarily, TAT variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, TAT variant polypeptides will have no more than one conservative amino acid substitution as compared to the native TAT polypeptide sequence, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native TAT polypeptide sequence.

[0045] "Percent (%) amino acid sequence identity" with respect to the TAT polypeptide sequences identified herein

is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific TAT polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0046] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "TAT", wherein "TAT" represents the amino acid sequence of a hypothetical TAT polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "TAT" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0047] "TAT variant polynucleotide" or "TAT variant nucleic acid sequence" means a nucleic acid molecule which encodes a TAT polypeptide, preferably an active TAT polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Ordinarily, a TAT variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83 %, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

[0048] Ordinarily, TAT variant polynucleotides are at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

[0049] "Percent (%) nucleic acid sequence identity" with respect to TAT-encoding nucleic acid sequences identified

herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the TAT nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0050] In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "TAT-DNA", wherein "TAT-DNA" represents a hypothetical TAT-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "TAT-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0051] In other embodiments, TAT variant polynucleotides are nucleic acid molecules that encode a TAT polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length TAT polypeptide as disclosed herein. TAT variant polypeptides may be those that are encoded by a TAT variant polynucleotide.

[0052] The term "full-length coding region" when used in reference to a nucleic acid encoding a TAT polypeptide refers to the sequence of nucleotides which encode the full-length TAT polypeptide of the invention (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures). The term "full-length coding region" when used in reference to an ATCC deposited nucleic acid refers to the TAT polypeptide-encoding portion of the cDNA that is inserted into the vector deposited with the ATCC (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

[0053] "Isolated," when used to describe the various TAT polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the TAT polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

[0054] An "isolated" TAT polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding

nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

[0055] The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[0056] Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[0057] "Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

[0058] "Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) overnight hybridization in a solution that employs 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with a 10 minute wash at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

[0059] "Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

[0060] The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a TAT polypeptide or anti-TAT antibody fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

[0061] "Active" or "activity" for the purposes herein refers to form(s) of a TAT polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring TAT, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring TAT other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT.

[0062] The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native TAT polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native TAT polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native TAT polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a TAT polypeptide

may comprise contacting a TAT polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the TAT polypeptide.

[0063] "Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. A subject or mammal is successfully "treated" for a TAT polypeptide-expressing cancer if, after receiving a therapeutic amount of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule according to the methods of the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition (i.e., slow to some extent and preferably stop) of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition (i.e., slow to some extent and preferably stop) of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. To the extent the anti-TAT antibody or TAT binding oligopeptide may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. Reduction of these signs or symptoms may also be felt by the patient.

[0064] The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR). Metastasis can be determined by staging tests and by bone scan and tests for calcium level and other enzymes to determine spread to the bone. CT scans can also be done to look for spread to the pelvis and lymph nodes in the area. Chest X-rays and measurement of liver enzyme levels by known methods are used to look for metastasis to the lungs and liver, respectively. Other routine methods for monitoring the disease include transrectal ultrasonography (TRUS) and transrectal needle biopsy (TRNB).

[0065] For bladder cancer, which is a more localized cancer, methods to determine progress of disease include urinary cytologic evaluation by cystoscopy, monitoring for presence of blood in the urine, visualization of the urothelial tract by sonography or an intravenous pyelogram, computed tomography (CT) and magnetic resonance imaging (MRI). The presence of distant metastases can be assessed by CT of the abdomen, chest x-rays, or radionuclide imaging of the skeleton.

[0066] "Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

[0067] "Mammal" for purposes of the treatment of, alleviating the symptoms of or diagnosis of a cancer refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

[0068] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

[0069] "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

[0070] By "solid phase" or "solid support" is meant a non-aqueous matrix to which an antibody, TAT binding oligopeptide or TAT binding organic molecule of the present invention can adhere or attach. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

[0071] A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a TAT polypeptide, an antibody thereto or a TAT binding oligopeptide) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

[0072] A "small" molecule or "small" organic molecule is defined herein to have a molecular weight below about 500 Daltons.

[0073] An "effective amount" of a polypeptide, antibody, TAT binding oligopeptide, TAT binding organic molecule or an agonist or antagonist thereof as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

[0074] The term "therapeutically effective amount" refers to an amount of an antibody, polypeptide, TAT binding oligopeptide, TAT binding organic molecule or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating". To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

[0075] A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule is an amount capable of inhibiting the growth of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

[0076] A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule is an amount capable of causing the destruction of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

[0077] The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-TAT monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-TAT antibody compositions with polypeptidic specificity, polyclonal antibodies, single chain anti-TAT antibodies, and fragments of anti-TAT antibodies (see below) as long as they exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

[0078] An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95 % by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

[0079] The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_{H1}). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

[0080] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0081] The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids

separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

[0082] The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H ; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H ; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

[0083] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991), for example.

[0084] The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

[0085] An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_{H1} , C_{H2} and C_{H3} . The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

[0086] "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0087] Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_{H1}). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_{H1} domain including one or more cysteines from the antibody hinge region. Pab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0088] The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

[0089] "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This

fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to

recognize and bind antigen, although at a lower affinity than the entire binding site.

[0090] "Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

[0091] The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that interchain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

[0092] "Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Opin. Struct. Biol.* 2:593-596 (1992).

[0093] A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

[0094] A "TAT binding oligopeptide" is an oligopeptide that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 81:3998-4002 (1984); Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 82:178-182 (1985); Geysen et al., in *Synthetic Peptides as Antigens*, 130-149 (1986); Geysen et al., *J. Immunol. Meth.*, 102:259-274 (1987); Schoofs et al., *J. Immunol.*, 140:611-616 (1988), Cwirla, S. E. et al. (1990) *Proc. Natl. Acad. Sci. USA*, 87:6378; Lowman, H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363, and Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668).

[0095] A "TAT binding organic molecule" is an organic molecule other than an oligopeptide or antibody as defined herein that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than

about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585).

[0096] An antibody, oligopeptide or other organic molecule "which binds" an antigen of interest, e.g. a tumor-associated polypeptide antigen target, is one that binds the antigen with sufficient affinity such that the antibody, oligopeptide or other organic molecule is useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody, oligopeptide or other organic molecule to a "non-target" protein will be less than about 10% of the binding of the antibody, oligopeptide or other organic molecule to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody, oligopeptide or other organic molecule to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a K_d for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

[0097] An antibody, oligopeptide or other organic molecule that "inhibits the growth of tumor cells expressing a TAT polypeptide" or a "growth inhibitory" antibody, oligopeptide or other organic molecule is one which results in measurable growth inhibition of cancer cells expressing or overexpressing the appropriate TAT polypeptide. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferred growth inhibitory anti-TAT antibodies, oligopeptides or organic molecules inhibit growth of TAT-expressing tumor cells by greater than 20 %, preferably from about 20 % to about 50%, and even more preferably, by greater than 50 % (e.g., from about 50% to about 100%) as compared to the appropriate control, the control typically being tumor cells not treated with the antibody, oligopeptide or other organic molecule being tested. In one embodiment, growth inhibition can be measured at an antibody concentration of about 0.1 to 30 μ g/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. Growth inhibition of tumor cells *in vivo* can be determined in various ways such as is described in the Experimental Examples section below. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1 μ g/kg to about 100 mg/kg body weight results in reduction in tumor size or tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

[0098] An antibody, oligopeptide or other organic molecule which "induces apoptosis" is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is usually one which overexpresses a TAT polypeptide. Preferably the cell is a tumor cell, e.g., a prostate, breast, ovarian, stomach, endometrial, lung, kidney, colon, bladder cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody, oligopeptide or other organic molecule which induces apoptosis is one which results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

[0099] Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0100] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently

kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes et al. (USA) 95:652-656 (1998).

[0101] "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an "activating receptor") and Fc γ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9: 457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

[0102] "Human effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least Fc γ RIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

[0103] "Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

[0104] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, multiple myeloma and B-cell lymphoma, brain, as well as head and neck cancer, and associated metastases.

[0105] The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are associated with some degree of abnormal cell proliferation. In one embodiment, the cell proliferative disorder is cancer.

[0106] "Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

[0107] An antibody, oligopeptide or other organic molecule which "induces cell death" is one which causes a viable cell to become nonviable. The cell is one which expresses a TAT polypeptide, preferably a cell that overexpresses a TAT polypeptide as compared to a normal cell of the same tissue type. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferably, the cell is a cancer cell, e.g., a breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. Cell death *in vitro* may be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death may be performed using heat inactivated serum (i.e., in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody, oligopeptide or other organic molecule is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. Cytotechnology 17:1-11 (1995)) or 7AAD can be assessed relative to untreated cells. Preferred cell death-inducing antibodies, oligopeptides or other organic molecules are those which induce PI uptake in the PI uptake assay in BT474 cells.

[0108] A "TAT-expressing cell" is a cell which expresses an endogenous or transfected TAT polypeptide either on the

cell surface or in a secreted form. A "TAT-expressing cancer" is a cancer comprising cells that have a TAT polypeptide present on the cell surface or that produce and secrete a TAT polypeptide. A "TAT-expressing cancer" optionally produces sufficient levels of TAT polypeptide on the surface of cells thereof, such that an anti-TAT antibody, oligopeptide or other organic molecule can bind thereto and have a therapeutic effect with respect to the cancer. In another embodiment, a "TAT-expressing cancer" optionally produces and secretes sufficient levels of TAT polypeptide, such that an anti-TAT antibody, oligopeptide or other organic molecule antagonist can bind thereto and have a therapeutic effect with respect to the cancer. With regard to the latter, the antagonist may be an antisense oligonucleotide which reduces, inhibits or prevents production and secretion of the secreted TAT polypeptide by tumor cells. A cancer which "overexpresses" a TAT polypeptide is one which has significantly higher levels of TAT polypeptide at the cell surface thereof, or produces and secretes, compared to a noncancerous cell of the same tissue type. Such overexpression may be caused by gene amplification or by increased transcription or translation. TAT polypeptide overexpression may be determined in a diagnostic or prognostic assay by evaluating increased levels of the TAT protein present on the surface of a cell, or secreted by the cell (e.g., via an immunohistochemistry assay using anti-TAT antibodies prepared against an isolated TAT polypeptide which may be prepared using recombinant DNA technology from an isolated nucleic acid encoding the TAT polypeptide; FACS analysis, etc.). Alternatively, or additionally, one may measure levels of TAT polypeptide-encoding nucleic acid or mRNA in the cell, e.g., via fluorescent *in situ* hybridization using a nucleic acid based probe corresponding to a TAT-encoding nucleic acid or the complement thereof; (FISH; see WO98/45479 published October, 1998), Southern blotting, Northern blotting, or polymerase chain reaction (PCR) techniques, such as real time quantitative PCR (RT-PCR). One may also study TAT polypeptide overexpression by measuring shed antigen in a biological fluid such as serum, e.g., using antibody-based assays (see also, e.g., U.S. Patent No. 4,933,294 issued June 12, 1990; WO91/05264 published April 18, 1991; U.S. Patent 5,401,638 issued March 28, 1995; and Sias et al., J. Immunol. Methods 132:73-80 (1990)). Aside from the above assays, various *in vivo* assays are available to the skilled practitioner. For example, one may expose cells within the body of the patient to an antibody which is optionally labeled with a detectable label, e.g., a radioactive isotope, and binding of the antibody to cells in the patient can be evaluated, e.g., by external scanning for radioactivity or by analyzing a biopsy taken from a patient previously exposed to the antibody.

[0109] As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesion part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

[0110] The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody, oligopeptide or other organic molecule so as to generate a "labeled" antibody, oligopeptide or other organic molecule. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

[0111] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³² and radioactive isotopes of Lu), chemotherapeutic agents e.g. methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

[0112] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a TAT-expressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of TAT-expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization,

which results in the inhibition of mitosis in cells.

[0113] "Doxorubicin" is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

[0114] The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon - α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF-B; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

[0115] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

Table 1

```

/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define _M      -8      /* value of a match with a stop */

int      _day[26][26] = {
/*      A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */ { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0, _M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */ { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2, _M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */ {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4, _M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */ { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2, _M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */ { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1, _M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
/* F */ {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4, _M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */ { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0, _M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */ {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2, _M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */ {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2, _M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */ {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1, _M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */ {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3, _M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */ {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2, _M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */ { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2, _M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1, _M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */ { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1, _M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */ {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0, _M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */ { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1, _M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
/* T */ { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0, _M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2, _M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */ {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4, _M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */ {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2, _M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */ { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1, _M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};

```

Table 1 (cont')

```

/*
*/
#include <stdio.h>
#include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

#define DMAT         3      /* value of matching bases */
#define DMIS         0      /* penalty for mismatched bases */
#define DINS0        8      /* penalty for a gap */
#define DINS1        1      /* penalty per base */
#define PINS0        8      /* penalty for a gap */
#define PINS1        4      /* penalty per residue */

struct jmp {
    short          n[MAXJMP]; /* size of jmp (neg for dely) */
    unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
}; /* limits seq to 2^16 -1 */

struct diag {
    int            score;      /* score at last jmp */
    long           offset;     /* offset of prev block */
    short          ijmp;       /* current jmp index */
    struct jmp      jmp;       /* list of jmps */
};

struct path {
    int            spc;        /* number of leading spaces */
    short          n[JMPS]; /* size of jmp (gap) */
    int            x[JMPS]; /* loc of jmp (last elem before gap) */
};

char             *ofile;      /* output file name */
char             *namex[2];   /* seq names: getseqs() */
char             *prog;       /* prog name for err msgs */
char             *seqx[2];    /* seqs: getseqs() */
int              dmax;        /* best diag: nw() */
int              dmax0;       /* final diag */
int              dna;         /* set if dna: main() */
int              endgaps;     /* set if penalizing end gaps */
int              gapx, gapy;   /* total gaps in seqs */
int              len0, len1;   /* seq lens */
int              ngapx, ngapy; /* total size of gaps */
int              smax;        /* max score: nw() */
int              *xbm;        /* bitmap for matching */
long             offset;      /* current offset in jmp file */
struct diag      *dx;         /* holds diagonals */
struct path      pp[2];       /* holds path for seqs */

char             *calloc(), *malloc(), *index(), *strcpy();
char             *getseq(), *g_calloc();

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
* Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
#include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
int ac;
char *av[];
{
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0; /* 1 to penalize endgaps */
    ofile = "align.out"; /* output file */

    nw(); /* fill in the matrix, get the possible jumps */
    readjumps(); /* get the actual jumps */
    print(); /* print stats, alignment */

    cleanup(0); /* unlink any tmp files */
}

```

main

Table 1 (cont')

```

5  /* do the alignment, return best score: main()
   * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
   * pro: PAM 250 values
   * When scores are equal, we prefer mismatches to any gap, prefer
   * a new gap to extending an ongoing gap, and prefer a gap in seqx
   * to a gap in seq y.
   */
10 nw()
   {
       char      *px, *py;           /* seqs and ptrs */
       int        *ndely, *dely;     /* keep track of dely */
       int        ndelx, delx;       /* keep track of delx */
       int        *tmp;              /* for swapping row0, row1 */
15      int        mis;               /* score for each type */
       int        ins0, ins1;        /* insertion penalties */
       register   id;                /* diagonal index */
       register   ij;               /* jmp index */
       register   *col0, *col1;      /* score for curr, last row */
       register   xx, yy;            /* index into seqs */
20
       dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

       ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
       dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
       col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
25      col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
       ins0 = (dna)? DINS0 : PINS0;
       ins1 = (dna)? DINS1 : PINS1;

       smax = -10000;
       if (endgaps) {
30         for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
             col0[yy] = dely[yy] = col0[yy-1] - ins1;
             ndely[yy] = yy;
         }
         col0[0] = 0;           /* Waterman Bull Math Biol 84 */
       }
35      else
         for (yy = 1; yy <= len1; yy++)
             dely[yy] = -ins0;

       /* fill in match matrix
        */
40      for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
         /* initialize first entry in col
          */
         if (endgaps) {
             if (xx == 1)
                 col1[0] = delx = -(ins0+ins1);
45             else
                 col1[0] = delx = col0[0] - ins1;
             ndelx = xx;
         }
         else {
50             col1[0] = 0;
             delx = -ins0;
             ndelx = 0;
         }
       }
55

```

Table 1 (cont')

```

5  for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

10  /* update penalty for del in x seq;
    * favor new del over ongoing del
    * ignore MAXGAP if weighting endgaps
    */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
15         dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
20  } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
25  }

    /* update penalty for del in y seq;
    * favor new del over ongoing del
    */
    if (endgaps || ndelx < MAXGAP) {
30         if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
35  } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
40  }

    /* pick the maximum score; we're favoring
    * mis over any del and delx over dely
    */
45
50
55

```

Table 1 (cont')

...nw

```

5      id = xx - yy + len1 - 1;
      if (mis >= delx && mis >= dely[yy])
          col1[yy] = mis;
      else if (delx >= dely[yy]) {
          col1[yy] = delx;
          ij = dx[id].ijmp;
10      if (dx[id].jp.n[0] && (1dna || (ndelx >= MAXJMP
          && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
              dx[id].ijmp++;
              if (++ij >= MAXJMP) {
                  writejumps(id);
                  ij = dx[id].ijmp = 0;
15              dx[id].offset = offset;
                  offset += sizeof(struct jmp) + sizeof(offset);
              }
              dx[id].jp.n[ij] = ndelx;
              dx[id].jp.x[ij] = xx;
              dx[id].score = delx;
20      }
      else {
          col1[yy] = dely[yy];
          ij = dx[id].ijmp;
      if (dx[id].jp.n[0] && (1dna || (ndely[yy] >= MAXJMP
25      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
              dx[id].ijmp++;
              if (++ij >= MAXJMP) {
                  writejumps(id);
                  ij = dx[id].ijmp = 0;
                  dx[id].offset = offset;
                  offset += sizeof(struct jmp) + sizeof(offset);
30              }
              dx[id].jp.n[ij] = -ndely[yy];
              dx[id].jp.x[ij] = xx;
              dx[id].score = dely[yy];
          }
35      if (xx == len0 && yy < len1) {
          /* last col
          */
          if (endgaps)
              col1[yy] -= ins0 + ins1*(len1-yy);
          if (col1[yy] > smax) {
40              smax = col1[yy];
              dmax = id;
          }
      }
    }
    if (endgaps && xx < len0)
60      col1[yy-1] -= ins0 + ins1*(len0-xx);
    if (col1[yy-1] > smax) {
        smax = col1[yy-1];
        dmax = id;
    }
    tmp = col0; col0 = col1; col1 = tmp;
50 }
(void) free((char *)ndcly);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);
}

```

Table 1 (cont')

```

/*
5  *
  * print() -- only routine visible outside this module
  *
  * static:
  * getmat() -- trace back best path, count matches: print()
  * pr_align() -- print alignment of described in array p[]: print()
10  * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
  * nums() -- put out a number line: dumpblock()
  * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
  * stars() -- put a line of stars: dumpblock()
  * stripname() -- strip any path and prefix from a seqname
  */

15  #include "nw.h"

  #define SPC      3
  #define P_LINE  256 /* maximum output line */
  #define P_SPC    3   /* space between name or num and seq */

20  extern _day[26][26];
  int olen; /* set output line length */
  FILE *fx; /* output file */

  print() print
25  {
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
      fprintf(stderr, "%s: can't write %s\n", prog, ofile);
      cleanup(1);
30    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
35    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
      pp[0].spc = firstgap = len1 - dmax - 1;
      ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
40      pp[1].spc = firstgap = dmax - (len1 - 1);
      lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
      lastgap = len0 - dmax0 - 1;
      lx -= lastgap;
45    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
      lastgap = dmax0 - (len0 - 1);
      ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
50  }

```

Table 1 (cont')

```

5  /*
   * trace back the best path, count matches
   */
static
getmat(lx, ly, firstgap, lastgap)                                getmat
    int    lx, ly;                /* "core" (minus endgaps) */
    int    firstgap, lastgap;     /* leading trailing overlap */
10 {
    int    nm, i0, i1, siz0, siz1;
    char    outx[32];
    double    pct;
    register    n0, n1;
    register char    *p0, *p1;
15
    /* get total matches, score
    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
20    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
25            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
            p0++;
            n0++;
            siz1--;
30        }
        else {
            if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
40        }
    }

    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
45    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
50    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);

```


Table 1 (cont')

```

5      fprintf(fx, "< gaps in first sequence: %d", gapx);
      if (gapx) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapx, (dna)? "base":"residue", (ngapx == 1)? ":" : "s");
          fprintf(fx, "%s", outx);

10     fprintf(fx, ", gaps in second sequence: %d", gapy);
      if (gapy) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapy, (dna)? "base":"residue", (ngapy == 1)? ":" : "s");
          fprintf(fx, "%s", outx);
      }
15     if (dna)
        fprintf(fx,
            "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
20         "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
            "< endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base" : "residue", (firstgap == 1)? ":" : "s",
25         lastgap, (dna)? "base" : "residue", (lastgap == 1)? ":" : "s");
    else
        fprintf(fx, "< endgaps not penalized\n");
}

static      nm;          /* matches in core -- for checking */
static      lmax;        /* lengths of stripped file names */
30 static      ij[2];      /* jmp index for a path */
static      nc[2];        /* number at start of current line */
static      ni[2];        /* current elem number -- for gapping */
static      siz[2];
static char  *ps[2];      /* ptr to current element */
static char  *po[2];      /* ptr to next output char slot */
35 static char out[2][P_LINE]; /* output line */
static char  star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
40 static
pr_align()
{
    int      nn;          /* char count */
    int      more;
45     register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(name[i]);
        if (nn > lmax)
            lmax = nn;

50         nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }
55

```

...getmat

pr_align

Table 1 (cont')

```

5      for (nn = nm = 0, more = 1; more; ) {
        for (i = more = 0; i < 2; i++) {
            /*
            * do we have more of this sequence?
            */
10         if (!*ps[i])
            continue;

            more++;

            if (pp[i].spc) { /* leading space */
15                 *po[i]++ = ' ';
                pp[i].spc--;
            }
            else if (siz[i]) { /* in a gap */
                *po[i]++ = '-';
                siz[i]--;
            }
20         else { /* we're putting a seq element
                    */
                *po[i] = *ps[i];
                if (islower(*ps[i]))
                    *ps[i] = toupper(*ps[i]);
                po[i]++;
                ps[i]++;

                /*
                * are we at next gap for this seq?
                */
30                 if (ni[i] == pp[i].x[ij[i]]) {
                    /*
                    * we need to merge all gaps
                    * at this location
                    */
                    siz[i] = pp[i].n[ij[i] + +];
                    while (ni[i] == pp[i].x[ij[i]])
                        siz[i] += pp[i].n[ij[i] + +];
35                 }
                ni[i]++;
            }
        }
        if (++nm == olen || !more && nn) {
40             dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nm = 0;
        }
    }
45 }

/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
static
50 dumpblock()
{
    register i;

    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
55

```

...pr_align

dumpblock

Table 1 (cont')**...dumpblock**

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
10              if (i == 0 && *out[1])
                  stars();
                  putline(i);
                  if (i == 0 && *out[1])
                      fprintf(fx, star);
15              if (i == 1)
                  nums(i);
          }
      }
}

/*
20  * put out a number line: dumpblock()
  */
static
nums(ix)                                nums
{
    int      ix;      /* index in out[] holding seq line */
25    char      nline[P_LINE];
    register  i, j;
    register char *pn, *px, *py;

    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
30    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
35                for (px = pn; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
40                i++;
        }
    }
    *pn = '\0';
    nc[ix] = i;
45    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
}

/*
50  * put out a line (name, [num], seq, [num]): dumpblock()
  */
static
putline(ix)                                putline
    int      ix;      {
55

```

Table 1 (cont')

...putline

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
10         (void) putc(*px, fx);
      for (; i < lmax+P_SPC; i++)
         (void) putc(' ', fx);

      /* these count from 1:
       * ni[] is current element (from 1)
       * nc[] is number at start of current line
       */
15      for (px = out[ix]; *px; px++)
         (void) putc(*px&0x7F, fx);
      (void) putc('\n', fx);
}

20

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
static
25 stars()
{
    int          i;
    register char *p0, *p1, cx, *px;

    if (!*out[0] || (*out[0] == ' ' && *(p0[0]) == ' ') ||
30     !*out[1] || (*out[1] == ' ' && *(p0[1]) == ' '))
        return;
    px = star;
    for (i = lmax+P_SPC; i; i--)
        *px++ = ' ';

35     for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
        if (isalpha(*p0) && isalpha(*p1)) {
            if (xbm[*p0-'A']&xbm[*p1-'A']) {
                cx = '*';
                nm++;
40             }
            else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                cx = '.';
            else
                cx = ' ';
        }
45     else
        cx = ' ';
        *px++ = cx;
    }
    *px++ = '\n';
    *px = '\0';
50 }

```

stars

Table 1 (cont')

```

/*
 * strip path or prefix from pn, return len; pr_align()
 */
static
stripname(pn)
    char    *pn;    /* file name (may be path) */
{
    register char    *px, *py;

    py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;

    if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}

```

stripname

Table 1 (cont')

```

5  /*
   * cleanup() -- cleanup any tmp file
   * getseq() -- read in seq, set dna, len, maxlen
   * g_calloc() -- calloc() with error checkin
   * readjumps() -- get the good jumps, from tmp file if necessary
   * writejumps() -- write a filled array of jumps to a tmp file: nw()
   */
10 #include "nw.h"
   #include <sys/file.h>

   char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
   FILE     *fj;

15   int      cleanup();                          /* cleanup tmp file */
   long     lseek();

   /*
   * remove any tmp file if we blow
   */
20 cleanup(i)
       int    i;
   {
       if (fj)
           (void) unlink(jname);
       exit(i);
25   }

   /*
   * read, return ptr to seq, set dna, len, maxlen
   * skip lines starting with ';', '<', or '>'
   * seq in upper or lower case
   */
30   char    *
   getseq(file, len)
       char    *file;          /* file name */
       int     *len;           /* seq len */
   {
35       char    line[1024], *pseq;
       register char *px, *py;
       int      natgc, tlen;
       FILE     *fp;

       if ((fp = fopen(file, "r")) == 0) {
40           fprintf(stderr, "%s: can't read %s\n", prog, file);
           exit(1);
       }
       tlen = natgc = 0;
       while (fgets(line, 1024, fp)) {
45           if (*line == ';' || *line == '<' || *line == '>')
               continue;
           for (px = line; *px != '\n'; px++)
               if (isupper(*px) || islower(*px))
                   tlen++;
       }
       if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
50           fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
           exit(1);
       }
       pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

cleanup

getseq

Table 1 (cont')

...getseq

```

5      py = pseq + 4;
      *len = tlen;
      rewind(fp);

      while (fgets(line, 1024, fp)) {
          if (*line == ';' || *line == '<' || *line == '>')
10             continue;
          for (px = line; *px != '\n'; px++) {
              if (isupper(*px))
                  *py++ = *px;
              else if (islower(*px))
                  *py++ = toupper(*px);
15             if (index("ATGCU",*(py-1)))
                 natgc++;
          }
      }
      *py++ = '\0';
      *py = '\0';
20      (void) fclose(fp);
      dna = natgc > (tlen/3);
      return(pseq+4);
  }

  char *
25  g_alloc(msg, nx, sz)
      char *msg;          /* program, calling routine */
      int nx, sz;         /* number and size of elements */
  {
      char *px, *calloc();

30      if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
          if (*msg) {
              fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
              exit(1);
          }
      }
35      return(px);
  }

  /*
   * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
   */
40  readjmps()
  {
      int fd = -1;
      int siz, i0, i1;
      register i, j, xx;

45      if (!f) {
          (void) fclose(f);
          if ((fd = open(jname, O_RDONLY, 0)) < 0) {
              fprintf(stderr, "%s: can't open() %s\n", prog, jname);
              cleanup(1);
          }
50      }
      for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; i++) {
          while (1) {
              for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                  ;
          }
      }
55

```

g_alloc

readjmps

Table 1 (cont')**...readjumps**

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
10        }
            else
                break;
        }
        if (i >= JMPS) {
            fprintf(stderr, "%s: too many gaps in alignment\n", prog);
            cleanup(1);
15        }
        if (j >= 0) {
            siz = dx[dmax].jp.n[j];
            xx = dx[dmax].jp.x[j];
            dmax += siz;
            if (siz < 0) { /* gap in second seq */
20                pp[1].n[i1] = -siz;
                xx += siz;
                /* id = xx - yy + len1 - 1
                */
                pp[1].x[i1] = xx - dmax + len1 - 1;
                gapy++;
                ngapy -= siz;
25            /* ignore MAXGAP when doing endgaps */
                siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
                i1++;
            }
            else if (siz > 0) { /* gap in first seq */
30                pp[0].n[i0] = siz;
                pp[0].x[i0] = xx;
                gapx++;
                ngapx += siz;
            /* ignore MAXGAP when doing endgaps */
35                siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                i0++;
            }
        }
        else
            break;
    }

40    /* reverse the order of jumps
    */
    for (j = 0, i0--; j < i0; j++, i0--) {
        i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
        i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
45    }
    for (j = 0, i1--; j < i1; j++, i1--) {
        i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
        i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
    }
    if (fd >= 0)
50        (void) close(fd);
    if (fj) {
        (void) unlink(jname);
        fj = 0;
        offset = 0;
55    }
}

```


Table 1 (cont')

```

5  /*
   * write a filled jmp struct offset of the prev one (if any): nw()
   */
writejumps(ix)                                writejumps
{
    int    ix;
    char    *mktemp();
10     if (!fj) {
        if (mktemp(jname) < 0) {
            fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
            cleanup(1);
        }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
    }
20     (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}

```

Table 2

TAT	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

5 divided by 15 = 33.3%

Table 3

TAT	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

5 divided by 10 = 50%

Table 4

TAT-DNA	NNNNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

Table 5

TAT-DNA	NNNNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =

4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A. Anti-TAT Antibodies

[0116] In one embodiment, the present invention provides anti-TAT antibodies which may find use herein as therapeutic and/or diagnostic agents. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

[0117] Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

[0118] Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

2. Monoclonal Antibodies

[0119] Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256: 495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

[0120] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

[0121] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[0122] Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Virginia, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[0123] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

[0124] The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson et al., Anal. Biochem., 107:220 (1980).

[0125] Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal e.g." by i.p. injection of the cells into mice.

[0126] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

[0127] DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opinion in Immunol., 5:256-262 (1993) and Plückthun, Immunol. Revs. 130:151-188 (1992).

[0128] In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10: 779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res. 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

[0129] The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain (C_H and C_L) sequences for the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., Proc. Natl Acad. Sci. USA, 81:6851 (1984)), or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin polypeptide sequences can substitute for the constant domains

of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

3. Human and Humanized Antibodies

[0130] The anti-TAT antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

[0131] Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeven et al., *Science*, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0132] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody) when the antibody is intended for human therapeutic use. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al., *J. Immunol.* 151:2296 (1993); Chothia et al., *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta et al., *J. Immunol.* 151:2623 (1993)).

[0133] It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

[0134] Various forms of a humanized anti-TAT antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

[0135] As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results

in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno. 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; and WO 97/17852.

[0136] Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties.

[0137] Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

[0138] As discussed above, human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275).

4. Antibody fragments

[0139] In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to solid tumors.

[0140] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter et al., Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased *in vivo* half-life comprising a salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during *in vivo* use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. See Antibody Engineering, ed. Borrebaeck, supra. The antibody fragment may also be a "linear antibody", e.g., as described in U.S. Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

5. Bispecific Antibodies

[0141] Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a TAT protein as described herein. Other such antibodies may combine a TAT binding site with a binding site for another protein. Alternatively, an anti-TAT arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD3), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), so as to focus and localize cellular defense mechanisms to the TAT-expressing cell. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express TAT. These antibodies possess a TAT-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon-α, vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')₂ bispecific antibodies).

[0142] WO 96/16673 describes a bispecific anti-ErbB2/anti-FcγRIII antibody and U.S. Patent No. 5,837,234 discloses a bispecific anti-ErbB2/anti-FcγRI antibody. A bispecific anti-ErbB2/Fcα antibody is shown in WO98/02463. U.S. Patent No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody.

[0143] Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., Nature 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., EMBO J. 10:3655-3659 (1991).

[0144] According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. Preferably, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant affect on the yield of the desired chain combination.

[0145] In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology 121:210 (1986).

[0146] According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

[0147] Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

[0148] Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

[0149] Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

[0150] Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the pro-

duction of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a V_H connected to a V_L by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., J. Immunol., 152:5368 (1994).

[0151] Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

6. Heteroconjugate Antibodies

[0152] Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

7. Multivalent Antibodies

[0153] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein comprises (or consists of) three to about eight, but preferably four, antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise $VD1-(X1)_n-VD2-(X2)_n-Fc$, wherein $VD1$ is a first variable domain, $VD2$ is a second variable domain, Fc is one polypeptide chain of an Fc region, $X1$ and $X2$ represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: $VH-CH1-flexible\ linker-VH-CH1-Fc$ region chain; or $VH-CH1-VH-CH1-Fc$ region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

8. Effector Function Engineering

[0154] It may be desirable to modify the antibody of the invention with respect to effector function, e.g., so as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp. Med. 176:1191-1195 (1992) and Shopes, B. J. Immunol. 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., Cancer Research 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design 3:219-230 (1989). To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

9. Immunoconjugates

[0155] The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

[0156] Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re . Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyantobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

[0157] Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, maytansinoids, a trichothene, and CC1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

Maytansine and maytansinoids

[0158] In one preferred embodiment, an anti-TAT antibody (full length or fragments) of the invention is conjugated to one or more maytansinoid molecules.

[0159] Maytansinoids are mitototic inhibitors which act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Patent No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Patent No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Patent Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, the disclosures of which are hereby expressly incorporated by reference.

Maytansinoid-antibody conjugates

[0160] In an attempt to improve their therapeutic index, maytansine and maytansinoids have been conjugated to antibodies specifically binding to tumor cell antigens. Immunoconjugates containing maytansinoids and their therapeutic use are disclosed, for example, in U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1, the disclosures of which are hereby expressly incorporated by reference. Liu et al., Proc. Natl. Acad. Sci. USA 93:8618-8623 (1996) described immunoconjugates comprising a maytansinoid designated DM1 linked to the monoclonal antibody C242 directed against human colorectal cancer. The conjugate was found to be highly cytotoxic towards cultured colon cancer cells, and showed antitumor activity in an *in vivo* tumor growth assay. Chari et al., Cancer Research 52:127-131 (1992) describe immunoconjugates in which a maytansinoid was conjugated via a disulfide linker to the murine antibody A7 binding to an antigen on human colon cancer cell lines, or to another murine monoclonal antibody TA. 1 that binds the HER-2/*neu* oncogene. The cytotoxicity of the TA.1-maytansinoid conjugate was tested *in vitro* on the human breast cancer cell line SK-BR-3, which expresses 3×10^5 HER-2 surface antigens per cell. The drug conjugate achieved a degree of cytotoxicity similar to the free maytansinoid drug, which could be increased by increasing the number of maytansinoid molecules per antibody molecule. The A7-maytansinoid conjugate showed low systemic cytotoxicity in mice.

Anti-TAT polypeptide antibody-maytansinoid conjugates (immunoconjugates)

[0161] Anti-TAT antibody-maytansinoid conjugates are prepared by chemically linking an anti-TAT antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the maytansinoid molecule. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule

of toxin/antibody would be expected to enhance cytotoxicity over the use of naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U. S. Patent No. 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Preferred maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters.

[0162] There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Patent No. 5,208,020 or EP Patent 0 425 235 B1, and Chari et al., Cancer Research 52:127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

[0163] Conjugates of the antibody and maytansinoid may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particularly preferred coupling agents include N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) (Carlsson et al., Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) to provide for a disulfide linkage.

[0164] The linker may be attached to the maytansinoid molecule at various positions, depending on the type of the link. For example, an ester linkage may be formed by reaction with a hydroxyl group using conventional coupling techniques. The reaction may occur at the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group, and the C-20 position having a hydroxyl group. In a preferred embodiment, the linkage is formed at the C-3 position of maytansinol or a maytansinol analogue.

Calicheamicin

[0165] Another immunoconjugate of interest comprises an anti-TAT antibody conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. patents 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I , α_2^I , α_3^I , N-acetyl- γ_1^I PSAG and θ_1^I (Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. patents to American Cyanamid). Another anti-tumor drug that the antibody can be conjugated is QFA which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

Other cytotoxic agents

[0166] Other antitumor agents that can be conjugated to the anti-TAT antibodies of the invention include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. patents 5,053,394, 5,770,710, as well as esperamicins (U.S. patent 5,877,296).

[0167] Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published October 28, 1993.

[0168] The present invention further contemplates an immunoconjugate formed between an antibody and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

[0169] For selective destruction of the tumor, the antibody may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated anti-TAT antibodies. Examples include At^{211} , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} , Pb^{212} and radioactive isotopes of Lu. When the conjugate is used for diagnosis, it may comprise a radioactive atom for scintigraphic studies, for example Tc^{99m} or I^{123} , or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0170] The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors

involving, for example, fluorine-19 in place of hydrogen. Labels such as ^{99m}Tc or ^{123}I , ^{186}Re , ^{188}Re and ^{111}In can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al (1978) Biochem. Biophys. Res. Commun. 80: 49-57) can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

[0171] Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile, linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., Cancer Research 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[0172] Alternatively, a fusion protein comprising the anti-TAT antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the conjugate.

[0173] In yet another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pre-targeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

10. Immunoliposomes

[0174] The anti-TAT antibodies disclosed herein may also be formulated as immunoliposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545; and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

[0175] Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem. 257:286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst. 81(19):1484 (1989).

B. TAT Binding Oligopeptides

[0176] TAT binding oligopeptides of the present invention are oligopeptides that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 82:178-182 (1985); Geysen et al., in Synthetic Peptides as Antigens, 130-149 (1986); Geysen et al., J. Immunol. Meth., 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. (1990) Proc. Natl. Acad. Sci. USA, 87:6378; Lowman,

H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363, and Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668).

[0177] In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large oligopeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a polypeptide target. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles (Scott, J.K. and Smith, G. P. (1990) *Science* 249: 386). The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly cloned cDNAs) can be rapidly and efficiently sorted for those sequences that bind to a target molecule with high affinity. Display of peptide (Cwirla, S. E. et al. (1990) *Proc. Natl. Acad. Sci. USA*, 87:6378) or protein (Lowman, H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363) libraries on phage have been used for screening millions of polypeptides or oligopeptides for ones with specific binding properties (Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668). Sorting phage libraries of random mutants requires a strategy for constructing and propagating a large number of variants, a procedure for affinity purification using the target receptor, and a means of evaluating the results of binding enrichments. U.S. Patent Nos. 5,223,409, 5,403,484, 5,571,689, and 5,663,143.

[0178] Although most phage display methods have used filamentous phage, lambdoid phage display systems (WO 95/34683; U.S. 5,627,024), T4 phage display systems (Ren, Z-J. et al. (1998) *Gene* 215:439; Zhu, Z. (1997) *CAN* 33: 534; Jiang, J. et al. (1997) *can* 128:44380; Ren, Z-J. et al. (1997) *CAN* 127:215644; Ren, Z-J. (1996) *Protein Sci.* 5: 1833; Efimov, V. P. et al. (1995) *Virus Genes* 10:173) and T7 phage display systems (Smith, G. P. and Scott, J.K. (1993) *Methods in Enzymology*, 217, 228-257; U.S. 5,766,905) are also known.

[0179] Many other improvements and variations of the basic phage display concept have now been developed. These improvements enhance the ability of display systems to screen peptide libraries for binding to selected target molecules and to display functional proteins with the potential of screening these proteins for desired properties. Combinatorial reaction devices for phage display reactions have been developed (WO 98/14277) and phage display libraries have been used to analyze and control bimolecular interactions (WO 98/20169; WO 98/20159) and properties of constrained helical peptides (WO 98/20036). WO 97/35196 describes a method of isolating an affinity ligand in which a phage display library is contacted with one solution in which the ligand will bind to a target molecule and a second solution in which the affinity ligand will not bind to the target molecule, to selectively isolate binding ligands. WO 97/46251 describes a method of biopanning a random phage display library with an affinity purified antibody and then isolating binding phage, followed by a micropanning process using microplate wells to isolate high affinity binding phage. The use of *Staphylococcus aureus* protein A as an affinity tag has also been reported (Li et al. (1998) *Mol Biotech.*, 9:187). WO 97/47314 describes the use of substrate subtraction libraries to distinguish enzyme specificities using a combinatorial library which may be a phage display library. A method for selecting enzymes suitable for use in detergents using phage display is described in WO 97/09446. Additional methods of selecting specific binding proteins are described in U.S. Patent Nos. 5,498,538, 5,432,018, and WO 98/15833.

[0180] Methods of generating peptide libraries and screening these libraries are also disclosed in U. S. Patent Nos. 5,723,286, 5,432,018, 5,580,717, 5,427,908, 5,498,530, 5,770,434, 5,734,018, 5,698,426, 5,763,192, and 5,723,323.

C. TAT Binding Organic Molecules

[0181] TAT binding organic molecules are organic molecules other than oligopeptides or antibodies as defined herein that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules may be, for example, aldehydes, ketones, oximes, hydrazones, semi-carbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides, or the like.

D. Screening for Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules With the Desired Properties

[0182] Techniques for generating antibodies, oligopeptides and organic molecules that bind to TAT polypeptides have been described above. One may further select antibodies, oligopeptides or other organic molecules with certain biological characteristics, as desired.

[0183] The growth inhibitory effects of an anti-TAT antibody, oligopeptide or other organic molecule of the invention may be assessed by methods known in the art, e.g., using cells which express a TAT polypeptide either endogenously or following transfection with the TAT gene. For example, appropriate tumor cell lines and TAT-transfected cells may be treated with an anti-TAT monoclonal antibody, oligopeptide or other organic molecule of the invention at various concentrations for a few days (e.g., 2-7) days and stained with crystal violet or MTT or analyzed by some other colorimetric assay. Another method of measuring proliferation would be by comparing ³H-thymidine uptake by the cells treated in the presence or absence of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule of the invention. After treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells *in vivo* can be determined in various ways known in the art. Preferably, the tumor cell is one that overexpresses a TAT polypeptide. Preferably, the anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule will inhibit cell proliferation of a TAT-expressing tumor cell *in vitro* or *in vivo* by about 25-100% compared to the untreated tumor cell, more preferably, by about 30-100%, and even more preferably by about 50-100% or 70-100%, in one embodiment, at an antibody concentration of about 0.5 to 30 µg/ml. Growth inhibition can be measured at an antibody concentration of about 0.5 to 30 µg/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1 µg/kg to about 100 mg/kg body weight results in reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

[0184] To select for an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule which induces cell death, loss of membrane integrity as indicated by, e.g., propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to control. A PI uptake assay can be performed in the absence of complement and immune effector cells. TAT polypeptide-expressing tumor cells are incubated with medium alone or medium containing the appropriate anti-TAT antibody (e.g., at about 10 µg/ml), TAT binding oligopeptide or TAT binding organic molecule. The cells are incubated for a 3 day time period. Following each treatment, cells are washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 µg/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those anti-TAT antibodies, TAT binding oligopeptides or TAT binding organic molecules that induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing anti-TAT antibodies, TAT binding oligopeptides or TAT binding organic molecules.

[0185] To screen for antibodies, oligopeptides or other organic molecules which bind to an epitope on a TAT polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if a test antibody, oligopeptide or other organic molecule binds the same site or epitope as a known anti-TAT antibody. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody to ensure proper folding. In a different method, peptides corresponding to different regions of a TAT polypeptide can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

E. Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT)

[0186] The antibodies of the present invention may also be used in ADEPT by conjugating the antibody to a prodrug-activating enzyme which converts a prodrug (e.g., a peptidyl chemotherapeutic agent, see WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Patent No. 4,975,278.

[0187] The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to convert it into its more active, cytotoxic form.

[0188] Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratio protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypepti-

dases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β -galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; β -lactamase useful for converting drugs derivatized with β -lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, Nature 328:457-458 (1987)). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme to a tumor cell population.

[0189] The enzymes of this invention can be covalently bound to the anti-TAT antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger et al., Nature 312:604-608 (1984)).

F. Full-Length TAT Polypeptides

[0190] The present invention also provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as TAT polypeptides. In particular, cDNAs (partial and full-length) encoding various TAT polypeptides have been identified and isolated, as disclosed in further detail in the Examples below.

[0191] As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the TAT polypeptides and encoding nucleic acids described herein, in some cases, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

G. Anti-TAT Antibody and TAT Polypeptide Variants

[0192] In addition to the anti-TAT antibodies and full-length native sequence TAT polypeptides described herein, it is contemplated that anti-TAT antibody and TAT polypeptide variants can be prepared. Anti-TAT antibody and TAT polypeptide variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the anti-TAT antibody or TAT polypeptide, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

[0193] Variations in the anti-TAT antibodies and TAT polypeptides described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the anti-TAT antibody or TAT polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the anti-TAT antibody or TAT polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

[0194] Anti-TAT antibody and TAT polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native antibody or protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the anti-TAT antibody or TAT polypeptide.

[0195] Anti-TAT antibody and TAT polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating antibody or polypeptide fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired antibody or polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define

the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, anti-TAT antibody and TAT polypeptide fragments share at least one biological and/or immunological activity with the native anti-TAT antibody or TAT polypeptide disclosed herein.

[0196] In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

[0197] Substantial modifications in function or immunological identity of the anti-TAT antibody or TAT polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

[0198] Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

[0199] The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13: 4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the anti-TAT antibody or TAT polypeptide variant DNA.

[0200] Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because

it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244:1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

[0201] Any cysteine residue not involved in maintaining the proper conformation of the anti-TAT antibody or TAT polypeptide also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-TAT antibody or TAT polypeptide to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

[0202] A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e. g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and human TAT polypeptide. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

[0203] Nucleic acid molecules encoding amino acid sequence variants of the anti-TAT antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-TAT antibody.

H. Modifications of Anti-TAT Antibodies and TAT Polypeptides

[0204] Covalent modifications of anti-TAT antibodies and TAT polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an anti-TAT antibody or TAT polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the anti-TAT antibody or TAT polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking anti-TAT antibody or TAT polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-TAT antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propionimide.

[0205] Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0206] Another type of covalent modification of the anti-TAT antibody or TAT polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the antibody or polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence anti-TAT antibody or TAT polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence anti-TAT antibody or TAT polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

[0207] Glycosylation of antibodies and other polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these

tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0208] Addition of glycosylation sites to the anti-TAT antibody or TAT polypeptide is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original anti-TAT antibody or TAT polypeptide (for O-linked glycosylation sites). The anti-TAT antibody or TAT polypeptide amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the anti-TAT antibody or TAT polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0209] Another means of increasing the number of carbohydrate moieties on the anti-TAT antibody or TAT polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

[0210] Removal of carbohydrate moieties present on the anti-TAT antibody or TAT polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

[0211] Another type of covalent modification of anti-TAT antibody or TAT polypeptide comprises linking the antibody or polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. The antibody or polypeptide also may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

[0212] The anti-TAT antibody or TAT polypeptide of the present invention may also be modified in a way to form chimeric molecules comprising an anti-TAT antibody or TAT polypeptide fused to another, heterologous polypeptide or amino acid sequence.

[0213] In one embodiment, such a chimeric molecule comprises a fusion of the anti-TAT antibody or TAT polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the anti-TAT antibody or TAT polypeptide. The presence of such epitope-tagged forms of the anti-TAT antibody or TAT polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the anti-TAT antibody or TAT polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

[0214] In an alternative embodiment, the chimeric molecule may comprise a fusion of the anti-TAT antibody or TAT polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of an anti-TAT antibody or TAT polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH₂ and CH₃, or the hinge, CH₁, CH₂ and CH₃ regions of an IgG molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

I. Preparation of Anti-TAT Antibodies and TAT Polypeptides

[0215] The description below relates primarily to production of anti-TAT antibodies and TAT polypeptides by culturing cells transformed or transfected with a vector containing anti-TAT antibody- and TAT polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-TAT antibodies and TAT polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may

be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the anti-TAT antibody or TAT polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired anti-TAT antibody or TAT polypeptide.

1. Isolation of DNA Encoding Anti-TAT Antibody or TAT Polypeptide

[0216] DNA encoding anti-TAT antibody or TAT polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the anti-TAT antibody or TAT polypeptide mRNA and to express it at a detectable level. Accordingly, human anti-TAT antibody or TAT polypeptide DNA can be conveniently obtained from a cDNA library prepared from human tissue. The anti-TAT antibody- or TAT polypeptide-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

[0217] Libraries can be screened with probes (such as oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding anti-TAT antibody or TAT polypeptide is to use PCR methodology [Sambrook et al., *supra*; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

[0218] Techniques for screening a cDNA library are well known in the art. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ^{32}P -labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., *supra*.

[0219] Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

[0220] Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

[0221] Host cells are transfected or transformed with expression or cloning vectors described herein for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., *supra*.

[0222] Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., *supra*, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

[0223] Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive

organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan^r*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan^r*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

[0224] Full length antibody, antibody fragments, and antibody fusion proteins can be produced in bacteria, in particular when glycosylation and Fc effector function are not needed, such as when the therapeutic antibody is conjugated to a cytotoxic agent (e.g., a toxin) and the immunoconjugate by itself shows effectiveness in tumor cell destruction. Full length antibodies have greater half life in circulation. Production in *E. coli* is faster and more cost efficient. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. 5,648,237 (Carter et al.), U.S. 5,789,199 (Joly et al.), and U.S. 5,840,523 (Simmons et al.) which describes translation initiation region (TIR) and signal sequences for optimizing expression and secretion, these patents incorporated herein by reference. After expression, the antibody is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., a protein A or G column depending on the isotype. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

[0225] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-TAT antibody- or TAT polypeptide-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112: 284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylophilic Yeasts, 269 (1982).

[0226] Suitable host cells for the expression of glycosylated anti-TAT antibody or TAT polypeptide are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells, such as cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

[0227] However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen. Virol. 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/DHFR (CHO, Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75);

human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0228] Host cells are transformed with the above-described expression or cloning vectors for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

3. Selection and Use of a Replicable Vector

[0229] The nucleic acid (e.g., cDNA or genomic DNA) encoding anti-TAT antibody or TAT polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

[0230] The TAT may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the anti-TAT antibody- or TAT polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

[0231] Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

[0232] Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

[0233] An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

[0234] Expression and cloning vectors usually contain a promoter operably linked to the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the *tac* promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding anti-TAT antibody or TAT polypeptide.

[0235] Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

[0236] Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled

by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

[0237] Anti-TAT antibody or TAT polypeptide transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

[0238] Transcription of a DNA encoding the anti-TAT antibody or TAT polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the anti-TAT antibody or TAT polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

[0239] Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-TAT antibody or TAT polypeptide.

[0240] Still other methods, vectors, and host cells suitable for adaptation to the synthesis of anti-TAT antibody or TAT polypeptide in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Culturing the Host Cells

[0241] The host cells used to produce the anti-TAT antibody or TAT polypeptide of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., Meth. Enz. 58:44 (1979), Barnes et al., Anal. Biochem. 102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

5. Detecting Gene Amplification/Expression

[0242] Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77: 5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

[0243] Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence TAT polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to TAT DNA and encoding a specific antibody epitope.

6. Purification of Anti-TAT Antibody and TAT Polypeptide

[0244] Forms of anti-TAT antibody and TAT polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of anti-TAT antibody and TAT polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

[0245] It may be desired to purify anti-TAT antibody and TAT polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the anti-TAT antibody and TAT polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, *Methods in Enzymology*, 182 (1990); Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular anti-TAT antibody or TAT polypeptide produced.

[0246] When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., *Bio/Technology* 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[0247] The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human $\gamma 1$, $\gamma 2$ or $\gamma 4$ heavy chains (Lindmark et al., *J. Immunol. Meth.* 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human $\gamma 3$ (Guss et al., *EMBO J.* 5:1567-1575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

[0248] Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

J. Pharmaceutical Formulations

[0249] Therapeutic formulations of the anti-TAT antibodies, TAT binding oligopeptides, TAT binding organic molecules and/or TAT polypeptides used in accordance with the present invention are prepared for storage by mixing the antibody, polypeptide, oligopeptide or organic molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's *Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, man-

nose, or dextrans; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG). The antibody preferably comprises the antibody at a concentration of between 5-200 mg/ml, preferably between 10-100 mg/ml.

[0250] The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-TAT antibody, TAT binding oligopeptide, or TAT binding organic molecule, it may be desirable to include in the one formulation, an additional antibody, e.g., a second anti-TAT antibody which binds a different epitope on the TAT polypeptide, or an antibody to some other target such as a growth factor that affects the growth of the particular cancer. Alternatively, or additionally, the composition may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0251] The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

[0252] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylenevinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT® (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

[0253] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

K. Diagnosis and Treatment with Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules

[0254] To determine TAT expression in the cancer, various diagnostic assays are available. In one embodiment, TAT polypeptide overexpression may be analyzed by immunohistochemistry (IHC). Paraffin embedded tissue sections from a tumor biopsy may be subjected to the IHC assay and accorded a TAT protein staining intensity criteria as follows:

Score 0 - no staining is observed or membrane staining is observed in less than 10 % of tumor cells.

Score 1+ - a faint/barely perceptible membrane staining is detected in more than 10 % of the tumor cells. The cells are only stained in part of their membrane.

Score 2+ - a weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.

Score 3+ - a moderate to strong complete membrane staining is observed in more than 10% of the tumor cells.

Those tumors with 0 or 1+ scores for TAT polypeptide expression may be characterized as not overexpressing TAT, whereas those tumors with 2+ or 3+ scores may be characterized as overexpressing TAT.

[0255] Alternatively, or additionally, FISH assays such as the INFORM® (sold by Ventana, Arizona) or PATHVISION® (Vysis, Illinois) may be carried out on formalin-fixed, paraffin-embedded tumor tissue to determine the extent (if any) of TAT overexpression in the tumor.

[0256] TAT overexpression or amplification may be evaluated using an *in vivo* diagnostic assay, e.g., by administering a molecule (such as an antibody, oligopeptide or organic molecule) which binds the molecule to be detected and is tagged with a detectable label (e.g., a radioactive isotope or a fluorescent label) and externally scanning the patient for localization of the label.

[0257] As described above, the anti-TAT antibodies, oligopeptides and organic molecules of the invention have various non-therapeutic applications. The anti-TAT antibodies, oligopeptides and organic molecules of the present invention can be useful for diagnosis and staging of TAT polypeptide-expressing cancers (e.g., in radioimaging). The antibodies, oligopeptides and organic molecules are also useful for purification or immunoprecipitation of TAT polypeptide from cells, for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot, to kill and eliminate TAT-expressing cells from a population of mixed cells as a step in the purification of other cells.

[0258] Currently, depending on the stage of the cancer, cancer treatment involves one or a combination of the following therapies: surgery to remove the cancerous tissue, radiation therapy, and chemotherapy. Anti-TAT antibody, oligopeptide or organic molecule therapy may be especially desirable in elderly patients who do not tolerate the toxicity and side

effects of chemotherapy well and in metastatic disease where radiation therapy has limited usefulness. The tumor targeting anti-TAT antibodies, oligopeptides and organic molecules of the invention are useful to alleviate TAT-expressing cancers upon initial diagnosis of the disease or during relapse. For therapeutic applications, the anti-TAT antibody, oligopeptide or organic molecule can be used alone, or in combination therapy with, e.g., hormones, antiangiogens, or radiolabelled compounds, or with surgery, cryotherapy, and/or radiotherapy. Anti-TAT antibody, oligopeptide or organic molecule treatment can be administered in conjunction with other forms of conventional therapy, either consecutively with, pre- or post-conventional therapy. Chemotherapeutic drugs such as TAXOTERE® (docetaxel), TAXOL® (paclitaxel), estramustine and mitoxantrone are used in treating cancer, in particular, in good risk patients. In the present method of the invention for treating or alleviating cancer, the cancer patient can be administered anti-TAT antibody, oligopeptide or organic molecule in conjunction with treatment with the one or more of the preceding chemotherapeutic agents. In particular, combination therapy with paclitaxel and modified derivatives (see, e.g., EP0600517) is contemplated. The anti-TAT antibody, oligopeptide or organic molecule will be administered with a therapeutically effective dose of the chemotherapeutic agent. In another embodiment, the anti-TAT antibody, oligopeptide or organic molecule is administered in conjunction with chemotherapy to enhance the activity and efficacy of the chemotherapeutic agent, e.g., paclitaxel. The Physicians' Desk Reference (PDR) discloses dosages of these agents that have been used in treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular cancer being treated, the extent of the disease and other factors familiar to the physician of skill in the art and can be determined by the physician.

[0259] In one particular embodiment, a conjugate comprising an anti-TAT antibody, oligopeptide or organic molecule conjugated with a cytotoxic agent is administered to the patient. Preferably, the immunoconjugate bound to the TAT protein is internalized by the cell, resulting in increased therapeutic efficacy of the immunoconjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent targets or interferes with the nucleic acid in the cancer cell. Examples of such cytotoxic agents are described above and include maytansinoids, calicheamicins, ribonucleases and DNA endonucleases.

[0260] The anti-TAT antibodies, oligopeptides, organic molecules or toxin conjugates thereof are administered to a human patient, in accord with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intra-synovial, intrathecal, oral, topical, or inhalation routes. Intravenous or subcutaneous administration of the antibody, oligopeptide or organic molecule is preferred.

[0261] Other therapeutic regimens may be combined with the administration of the anti-TAT antibody, oligopeptide or organic molecule. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preferably such combined therapy results in a synergistic therapeutic effect.

[0262] It may also be desirable to combine administration of the anti-TAT antibody or antibodies, oligopeptides or organic molecules, with administration of an antibody directed against another tumor antigen associated with the particular cancer.

[0263] In another embodiment, the therapeutic treatment methods of the present invention involves the combined administration of an anti-TAT antibody (or antibodies), oligopeptides or organic molecules and one or more chemotherapeutic agents or growth inhibitory agents, including co-administration of cocktails of different chemotherapeutic agents. Chemotherapeutic agents include estramustine phosphate, prednimustine, cisplatin, 5-fluorouracil, melphalan, cyclophosphamide, hydroxyurea and hydroxyureataxanes (such as paclitaxel and doxorubicin) and/or anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992).

[0264] The antibody, oligopeptide or organic molecule may be combined with an anti-hormonal compound; e.g., an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, in dosages known for such molecules. Where the cancer to be treated is androgen independent cancer, the patient may previously have been subjected to anti-androgen therapy and, after the cancer becomes androgen independent, the anti-TAT antibody, oligopeptide or organic molecule (and optionally other agents as described herein) may be administered to the patient.

[0265] Sometimes, it may be beneficial to also co-administer a cardioprotectant (to prevent or reduce myocardial dysfunction associated with the therapy) or one or more cytokines to the patient. In addition to the above therapeutic regimens, the patient may be subjected to surgical removal of cancer cells and/or radiation therapy, before, simultaneously with, or post antibody, oligopeptide or organic molecule therapy. Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and anti-TAT antibody, oligopeptide or organic molecule.

[0266] For the prevention or treatment of disease, the dosage and mode of administration will be chosen by the

physician according to known criteria. The appropriate dosage of antibody, oligopeptide or organic molecule will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody, oligopeptide or organic molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, oligopeptide or organic molecule, and the discretion of the attending physician. The antibody, oligopeptide or organic molecule is suitably administered to the patient at one time or over a series of treatments. Preferably, the antibody, oligopeptide or organic molecule is administered by intravenous infusion or by subcutaneous injections. Depending on the type and severity of the disease, about 1 $\mu\text{g/kg}$ to about 50 mg/kg body weight (e.g., about 0.1-15mg/kg/dose) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A dosing regimen can comprise administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the anti-TAT antibody. However, other dosage regimens may be useful. A typical daily dosage might range from about 1 $\mu\text{g/kg}$ to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. The progress of this therapy can be readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art.

[0267] Aside from administration of the antibody protein to the patient, the present application contemplates administration of the antibody by gene therapy. Such administration of nucleic acid encoding the antibody is encompassed by the expression "administering a therapeutically effective amount of an antibody". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

[0268] There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the site where the antibody is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g., U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retroviral vector.

[0269] The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). For review of the currently known gene marking and gene therapy protocols see Anderson et al., Science 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

[0270] The anti-TAT antibodies of the invention can be in the different forms encompassed by the definition of "antibody" herein. Thus, the antibodies include full length or intact antibody, antibody fragments, native sequence antibody or amino acid variants, humanized, chimeric or fusion antibodies, immunoconjugates, and functional fragments thereof. In fusion antibodies an antibody sequence is fused to a heterologous polypeptide sequence. The antibodies can be modified in the Fc region to provide desired effector functions. As discussed in more detail in the sections herein, with the appropriate Fc regions, the naked antibody bound on the cell surface can induce cytotoxicity, e.g., via antibody-dependent cellular cytotoxicity (ADCC) or by recruiting complement in complement dependent cytotoxicity, or some other mechanism. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, certain other Fc regions may be used.

[0271] In one embodiment, the antibody competes for binding or bind substantially to, the same epitope as the antibodies of the invention. Antibodies having the biological characteristics of the present anti-TAT antibodies of the invention are also contemplated, specifically including the *in vivo* tumor targeting and any cell proliferation inhibition or cytotoxic characteristics.

[0272] Methods of producing the above antibodies are described in detail herein.

[0273] The present anti-TAT antibodies, oligopeptides and organic molecules are useful for treating a TAT-expressing cancer or alleviating one or more symptoms of the cancer in a mammal. Such a cancer includes prostate cancer, cancer of the urinary tract, lung cancer, breast cancer, colon cancer and ovarian cancer, more specifically, prostate adenocarcinoma, renal cell carcinomas, colorectal adenocarcinomas, lung adenocarcinomas, lung squamous cell carcinomas, and pleural mesothelioma. The cancers encompass metastatic cancers of any of the preceding. The antibody, oligopeptide or organic molecule is able to bind to at least a portion of the cancer cells that express TAT polypeptide in the mammal. In a preferred embodiment, the antibody, oligopeptide or organic molecule is effective to destroy or kill TAT-expressing tumor cells or inhibit the growth of such tumor cells, *in vitro* or *in vivo*, upon binding to TAT polypeptide on the cell. Such an antibody includes a naked anti-TAT antibody (not conjugated to any agent). Naked antibodies that have cytotoxic or cell growth inhibition properties can be further harnessed with a cytotoxic agent to render them even

more potent in tumor cell destruction. Cytotoxic properties can be conferred to an anti-TAT antibody by, e.g., conjugating the antibody with a cytotoxic agent, to form an immunoconjugate as described herein. The cytotoxic agent or a growth inhibitory agent is preferably a small molecule. Toxins such as calicheamicin or a maytansinoid and analogs or derivatives thereof, are preferable.

[0274] The invention provides a composition comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. For the purposes of treating cancer, compositions can be administered to the patient in need of such treatment, wherein the composition can comprise one or more anti-TAT antibodies present as an immunoconjugate or as the naked antibody. In a further embodiment, the compositions can comprise these antibodies, oligopeptides or organic molecules in combination with other therapeutic agents such as cytotoxic or growth inhibitory agents, including chemotherapeutic agents. The invention also provides formulations comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. In one embodiment, the formulation is a therapeutic formulation comprising a pharmaceutically acceptable carrier.

[0275] Another aspect of the invention is isolated nucleic acids encoding the anti-TAT antibodies. Nucleic acids encoding both the H and L chains and especially the hypervariable region residues, chains which encode the native sequence antibody as well as variants, modifications and humanized versions of the antibody, are encompassed.

[0276] The invention also provides methods useful for treating a TAT polypeptide-expressing cancer or alleviating one or more symptoms of the cancer in a mammal, comprising administering a therapeutically effective amount of an anti-TAT antibody, oligopeptide or organic molecule to the mammal. The antibody, oligopeptide or organic molecule therapeutic compositions can be administered short term (acute) or chronic, or intermittent as directed by physician. Also provided are methods of inhibiting the growth of, and killing a TAT polypeptide-expressing cell.

[0277] The invention also provides kits and articles of manufacture comprising at least one anti-TAT antibody, oligopeptide or organic molecule. Kits containing anti-TAT antibodies, oligopeptides or organic molecules find use, e.g., for TAT cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For example, for isolation and purification of TAT, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT *in vitro*, e.g., in an ELISA or a Western blot. Such antibody, oligopeptide or organic molecule useful for detection may be provided with a label such as a fluorescent or radiolabel.

L. Articles of Manufacture and Kits

[0278] Another embodiment of the invention is an article of manufacture containing materials useful for the treatment of anti-TAT expressing cancer. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the cancer condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-TAT antibody, oligopeptide or organic molecule of the invention. The label or package insert indicates that the composition is used for treating cancer. The label or package insert will further comprise instructions for administering the antibody, oligopeptide or organic molecule composition to the cancer patient. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0279] Kits are also provided that are useful for various purposes, e.g., for TAT-expressing cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For isolation and purification of TAT polypeptide, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one anti-TAT antibody, oligopeptide or organic molecule of the invention. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended *in vitro* or diagnostic use.

M. Uses for TAT Polypeptides and TAT-Polypeptide Encoding Nucleic Acids

[0280] Nucleotide sequences (or their complement) encoding TAT polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA probes. TAT-encoding nucleic acid will also be useful for the preparation of TAT polypeptides

by the recombinant techniques described herein, wherein those TAT polypeptides may find use, for example, in the preparation of anti-TAT antibodies as described herein.

[0281] The full-length native sequence TAT gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length TAT cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of TAT or TAT from other species) which have a desired sequence identity to the native TAT sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence TAT. By way of example, a screening method will comprise isolating the coding region of the TAT gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ³²P or ³⁵S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the TAT gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below. Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

[0282] Other useful fragments of the TAT-encoding nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target TAT mRNA (sense) or TAT DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of TAT DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

[0283] Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. Such methods are encompassed by the present invention. The antisense oligonucleotides thus may be used to block expression of TAT proteins, wherein those TAT proteins may play a role in the induction of cancer in mammals. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91 /06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

[0284] Preferred intragenic sites for antisense binding include the region incorporating the translation initiation/start codon (5'-AUG / 5'-ATG) or termination/stop codon (5'-UAA, 5'-UAG and 5'-UGA / 5'-TAA, 5'-TAG and 5'-TGA) of the open reading frame (ORF) of the gene. These regions refer to a portion of the mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation or termination codon. Other preferred regions for antisense binding include: introns; exons; intron-exon junctions; the open reading frame (ORF) or "coding region," which is the region between the translation initiation codon and the translation termination codon; the 5' cap of an mRNA which comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage and includes 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap; the 5' untranslated region (5'UTR), the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene; and the 3' untranslated region (3'UTR), the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene.

[0285] Specific examples of preferred antisense compounds useful for inhibiting expression of TAT proteins include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotri-esters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and borano-phosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has

a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included. Representative United States patents that teach the preparation of phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos.: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated by reference.

[0286] Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Representative United States patents that teach the preparation of such oligonucleosides include, but are not limited to, U.S. Pat. Nos.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, each of which is herein incorporated by reference.

[0287] In other preferred antisense oligonucleotides, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos.: 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., Science, 1991, 254, 1497-1500.

[0288] Preferred antisense oligonucleotides incorporate phosphorothioate backbones and/or heteroatom backbones, and in particular -CH₂-NH-O-CH₂-, -CH₂-N(CH₃)-O-CH₂- [known as a methylene (methylimino) or MMI backbone], -CH₂-O-N(CH₃)-CH₂-, -CH₂-N(CH₃)-N(CH₃)-CH₂- and -O-N(CH₃)-CH₂-CH₂- [wherein the native phosphodiester backbone is represented as -O-P-O-CH₂-] described in the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are antisense oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

[0289] Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-alkyl, S-alkyl, or N-alkyl; O-alkenyl, S-alkenyl, or N-alkenyl; O-alkynyl, S-alkynyl or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Particularly preferred are O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. Other preferred antisense oligonucleotides comprise one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₃)₂.

[0290] A further preferred modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene (-CH₂-)_n group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

[0291] Other preferred modifications include 2'-methoxy (2'-O-CH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂), 2'-allyl (2'-CH₂-CH=CH₂), 2'-O-allyl (2'-O-CH₂-CH=CH₂) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the

preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, each of which is herein incorporated by reference in its entirety.

[0292] Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl ($-C\equiv C-CH_3$ or $-CH_2-CL=CH$) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoinidole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and those disclosed by Englisch et al., *Angewandte Chemie, International Edition*, 1991, 30, 613. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi et al, *Antisense Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Representative United States patents that teach the preparation of modified nucleobases include, but are not limited to: U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; 5,681,941 and 5,750,692, each of which is herein incorporated by reference.

[0293] Another modification of antisense oligonucleotides chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. The compounds of the invention can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugates groups include cholesterol, lipids, cation lipids, phospholipids, cationic phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen sequence-specific hybridization with RNA. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, 10, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxysterol moiety. Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobemoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an anti-

bacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) and United States patents Nos.: 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

[0294] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxyoligonucleotides hybridizing to the same target region. Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Preferred chimeric antisense oligonucleotides incorporate at least one 2' modified sugar (preferably 2'-O-(CH₂)₂-O-CH₃) at the 3' terminal to confer nuclease resistance and a region with at least 4 contiguous 2'-H sugars to confer RNase H activity. Such compounds have also been referred to in the art as hybrids or gapmers. Preferred gapmers have a region of 2' modified sugars (preferably 2'-O-(CH₂)₂-O-CH₃) at the 3'-terminal and at the 5' terminal separated by at least one region having at least 4 contiguous 2'-H sugars and preferably incorporate phosphorothioate backbone linkages. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference in its entirety.

[0295] The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

[0296] Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

[0297] Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO₄-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

[0298] Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding

molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

[0299] Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

[0300] Antisense or sense RNA or DNA molecules are generally at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

[0301] The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related TAT coding sequences.

[0302] Nucleotide sequences encoding a TAT can also be used to construct hybridization probes for mapping the gene which encodes that TAT and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

[0303] When the coding sequences for TAT encode a protein which binds to another protein (example, where the TAT is a receptor), the TAT can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor TAT can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native TAT or a receptor for TAT. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

[0304] Nucleic acids which encode TAT or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding TAT. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for TAT transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding TAT introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding TAT. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

[0305] Alternatively, non-human homologues of TAT can be used to construct a TAT "knock out" animal which has a defective or altered gene encoding TAT as a result of homologous recombination between the endogenous gene encoding TAT and altered genomic DNA encoding TAT introduced into an embryonic stem cell of the animal. For example, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques. A portion of the genomic DNA encoding TAT can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*,

E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the TAT polypeptide.

[0306] Nucleic acid encoding the TAT polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik et al., Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

[0307] There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et al., Trends in Biotechnology 11,205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

[0308] The nucleic acid molecules encoding the TAT polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each TAT nucleic acid molecule of the present invention can be used as a chromosome marker.

[0309] The TAT polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the TAT polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. TAT nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

[0310] This invention encompasses methods of screening compounds to identify those that mimic the TAT polypeptide (agonists) or prevent the effect of the TAT polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the TAT polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins, including e.g., inhibiting the expression of TAT polypeptide from cells. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

[0311] The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

[0312] All assays for antagonists are common in that they call for contacting the drug candidate with a TAT polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

[0313] In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the TAT polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the TAT polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the TAT polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored

component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

[0314] If the candidate compound interacts with but does not bind to a particular TAT polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, *Nature* (London), 340: 245-246 (1989); Chien et al., *Proc. Natl. Acad. Sci. USA*, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, *Proc. Natl. Acad. Sci. USA*, 89: 5789-5793(1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

[0315] Compounds that interfere with the interaction of a gene encoding a TAT polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

[0316] To assay for antagonists, the TAT polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the TAT polypeptide indicates that the compound is an antagonist to the TAT polypeptide. Alternatively, antagonists may be detected by combining the TAT polypeptide and a potential antagonist with membrane-bound TAT polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The TAT polypeptide can be labeled, such as by radioactivity, such that the number of TAT polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., *Current Protocols in Immun.*, 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the TAT polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the TAT polypeptide. Transfected cells that are grown on glass slides are exposed to labeled TAT polypeptide. The TAT polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

[0317] As an alternative approach for receptor identification, labeled TAT polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

[0318] In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled TAT polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

[0319] More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with TAT polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal anti-

bodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the TAT polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the TAT polypeptide.

[0320] Another potential TAT polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature TAT polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the TAT polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the TAT polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the TAT polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

[0321] Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the TAT polypeptide, thereby blocking the normal biological activity of the TAT polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

[0322] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

[0323] Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

[0324] These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

[0325] Isolated TAT polypeptide-encoding nucleic acid can be used herein for recombinantly producing TAT polypeptide using techniques well known in the art and as described herein. In turn, the produced TAT polypeptides can be employed for generating anti-TAT antibodies using techniques well known in the art and as described herein.

[0326] Antibodies specifically binding a TAT polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders, including cancer, in the form of pharmaceutical compositions.

[0327] If the TAT polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco et al., Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

[0328] The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0329] The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

[0330] All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

[0331] Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Tissue Expression Profiling Using GeneExpress®

[0332] A proprietary database containing gene expression information (GeneExpress®, Gene Logic Inc., Gaithersburg, MD) was analyzed in an attempt to identify polypeptides (and their encoding nucleic acids) whose expression is significantly upregulated in a particular tumor tissue(s) of interest as compared to other tumor(s) and/or normal tissues. Specifically, analysis of the GeneExpress® database was conducted using either software available through Gene Logic Inc., Gaithersburg, MD, for use with the GeneExpress® database or with proprietary software written and developed at Genentech, Inc. for use with the GeneExpress® database. The rating of positive hits in the analysis is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues.

[0333] Molecules whose tissue expression profile as determined from an analysis of the GeneExpress® database evidences high tissue expression and significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues are excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

EXAMPLE 2: Microarray Analysis to Detect Upregulation of TAT Polypeptides in Cancerous Tumors

[0334] Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of a probe from a control (normal tissue) sample, the gene or genes overexpressed in the disease tissue are identified. The implication of this result is that an overexpressed protein in a diseased tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

[0335] The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

[0336] In the present example, cancerous tumors derived from various human tissues were studied for upregulated gene expression relative to cancerous tumors from different tissue types and/or non-cancerous human tissues in an attempt to identify those polypeptides which are overexpressed in a particular cancerous tumor(s). In certain experiments, cancerous human tumor tissue and non-cancerous human tumor tissue of the same tissue type (often from the same patient) were obtained and analyzed for TAT polypeptide expression. Additionally, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test: control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.

[0337] In the present experiments, nucleic acid probes derived from the herein described TAT polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from various tumor tissues were used for the hybridization thereto. Below is shown the results of these experiments, demonstrating that various TAT polypeptides of the present invention are significantly overexpressed in various human tumor tissues as compared to their normal counterpart tissue(s). Moreover, all of the molecules shown below are significantly overexpressed in their specific tumor tissue(s) as compared to in the "universal" epithelial control. As described above, these data demonstrate that the TAT polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous

tumors, but also serve as therapeutic targets for the treatment of those tumors.

Molecule	upregulation of expression in:	as compared to:
DNA219894 (TAT211)	ovarian tumor	normal ovarian tissue
DNA219894 (TAT211)	lung tumor	normal lung tissue

EXAMPLE 3: Quantitative Analysis of TAT mRNA Expression

[0338] In this assay, a 5' nuclease assay (for example, TaqMan®) and real-time quantitative PCR (for example, ABI Prizm 7700 Sequence Detection System® (Perkin Elmer, Applied Biosystems Division, Foster City, CA)), were used to find genes that are significantly overexpressed in a cancerous tumor or tumors as compared to other cancerous tumors or normal non-cancerous tissue. The 5' nuclease assay reaction is a fluorescent PCR-based technique which makes use of the 5' exonuclease activity of Taq DNA polymerase enzyme to monitor gene expression in real time. Two oligo-nucleotide primers (whose sequences are based upon the gene or EST sequence of interest) are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe, is designed to detect nucleotide sequence located between the two PCR primers. The probe is non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the PCR amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second fluorophore. One molecule of reporter dye is liberated for each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

[0339] The 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI Prizm 7700TM Sequence Detection. The system consists of a thermocycler, laser, charge-coupled device (CCD) camera and computer. The system amplifies samples in a 96-well format on a thermocycler. During amplification, laser-induced fluorescent signal is collected in real-time through fiber optics cables for all 96 wells, and detected at the CCD. The system includes software for running the instrument and for analyzing the data.

[0340] The starting material for the screen was mRNA isolated from a variety of different cancerous tissues. The mRNA is quantitated precisely, e.g., fluorometrically. As a negative control, RNA was isolated from various normal tissues of the same tissue type as the cancerous tissues being tested.

[0341] 5' nuclease assay data are initially expressed as Ct, or the threshold cycle. This is defined as the cycle at which the reporter signal accumulates above the background level of fluorescence. The ΔC_t values are used as quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer mRNA results to normal human mRNA results. As one Ct unit corresponds to 1 PCR cycle or approximately a 2-fold relative increase relative to normal, two units corresponds to a 4-fold relative increase, 3 units corresponds to an 8-fold relative increase and so on, one can quantitatively measure the relative fold increase in mRNA expression between two or more different tissues. Using this technique, the molecules listed below have been identified as being significantly overexpressed in a particular tumor(s) as compared to their normal non-cancerous counterpart tissue(s) (from both the same and different tissue donors) and thus, represent excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

Molecule	upregulation of expression in:	as compared to:
DNA219894 (TAT211)	lung tumor	normal lung tissue

EXAMPLE 4: *In situ* Hybridization

[0342] *In situ* hybridization is a powerful and versatile technique for the detection and localization of nucleic acid sequences within cell or tissue preparations. It may be useful, for example, to identify sites of gene expression, analyze the tissue distribution of transcription, identify and localize viral infection, follow changes in specific mRNA synthesis and aid in chromosome mapping.

[0343] *In situ* hybridization was performed following an optimized version of the protocol by Lu and Gillett, Cell Vision 1:169-176 (1994), using PCR-generated ³³P-labeled riboprobes. Briefly, formalin-fixed, paraffin-embedded human tissues were sectioned, deparaffinized, deproteinized in proteinase K (20 g/ml) for 15 minutes at 37°C, and further processed for *in situ* hybridization as described by Lu and Gillett, *supra*. A [³³P] UTP-labeled antisense riboprobe was generated from a PCR product and hybridized at 55°C overnight. The slides were dipped in Kodak NTB2 nuclear track emulsion and exposed for 4 weeks.

³³P-Riboprobe synthesis

[0344] 6.0 µl (125 mCi) of ³³P-UTP (Amersham BF 1002, SA <2000 Ci/mmol) were speed vac dried. To each tube containing dried ³³P-UTP, the following ingredients were added:

- 2.0 µl 5x transcription buffer
- 1.0 µl DTT (100 mM)
- 2.0 µl NTP mix (2.5 mM : 10 µ; each of 10 mM GTP, CTP & ATP + 10 µl H₂O)
- 1.0 µl UTP (50 µM)
- 1.0 µl Rnasin
- 1.0 µl DNA template (1 µg)
- 1.0 µl H₂O
- 1.0 µl RNA polymerase (for PCR products T3 = AS, T7 = S, usually)

[0345] The tubes were incubated at 37°C for one hour. 1.0 µl RQ1 DNase were added, followed by incubation at 37°C for 15 minutes. 90 µl TE (10 mM Tris pH 7.6/1mM EDTA pH 8.0) were added, and the mixture was pipetted onto DE81 paper. The remaining solution was loaded in a Microcon-50 ultrafiltration unit, and spun using program 10 (6 minutes). The filtration unit was inverted over a second tube and spun using program 2 (3 minutes). After the final recovery spin, 100 µl TE were added. 1 µl of the final product was pipetted on DE81 paper and counted in 6 ml of Biofluor II.

[0346] The probe was run on a TBE/urea gel. 1-3 µl of the probe or 5 µl of RNA Mrk III were added to 3 µl of loading buffer. After heating on a 95°C heat block for three minutes, the probe was immediately placed on ice. The wells of gel were flushed, the sample loaded, and run at 180-250 volts for 45 minutes. The gel was wrapped in saran wrap and exposed to XAR film with an intensifying screen in -70°C freezer one hour to overnight.

³³P-HybridizationA. Pretreatment of frozen sections

[0347] The slides were removed from the freezer, placed on aluminium trays and thawed at room temperature for 5 minutes. The trays were placed in 55 °C incubator for five minutes to reduce condensation. The slides were fixed for 10 minutes in 4 % paraformaldehyde on ice in the fume hood, and washed in 0.5 x SSC for 5 minutes, at room temperature (25 ml 20 x SSC + 975 ml SQ H₂O). After deproteinization in 0.5 µg/ml proteinase K for 10 minutes at 37°C (12.5 µl of 10 mg/ml stock in 250 ml prewarmed RNase-free RNase buffer), the sections were washed in 0.5 x SSC for 10 minutes at room temperature. The sections were dehydrated in 70%, 95 %, 100 % ethanol, 2 minutes each.

B. Pretreatment of paraffin-embedded sections

[0348] The slides were deparaffinized, placed in SQ H₂O, and rinsed twice in 2 x SSC at room temperature, for 5 minutes each time. The sections were deproteinated in 20 µg/ml proteinase K (500 µl of 10 mg/ml in 250 ml RNase-free RNase buffer; 37 °C, 15 minutes) - human embryo, or 8 x proteinase K (100 µl in 250 ml Rnase buffer, 37°C, 30 minutes) - formalin tissues. Subsequent rinsing in 0.5 x SSC and dehydration were performed as described above.

C. Prehybridization

[0349] The slides were laid out in a plastic box lined with Box buffer (4 x SSC, 50% formamide) - saturated filter paper.

D. Hybridization

[0350] 1.0 x 10⁶ cpm probe and 1.0 µl tRNA (50 mg/ml stock) per slide were heated at 95 °C for 3 minutes. The slides were cooled on ice, and 48 µl hybridization buffer were added per slide. After vortexing, 50 µl ³³P mix were added to 50 µl prehybridization on slide. The slides were incubated overnight at 55°C.

E. Washes

[0351] Washing was done 2 x 10 minutes with 2xSSC, EDTA at room temperature (400 ml 20 x SSC + 16 ml 0.25M EDTA, V_f=4L), followed by RNaseA treatment at 37°C for 30 minutes (500 µl of 10 mg/ml in 250 ml Rnase buffer = 20 µg/ml), The slides were washed 2 x 10 minutes with 2 x SSC, EDTA at room temperature. The stringency wash conditions were as follows: 2 hours at 55 °C, 0.1 x SSC, EDTA (20 ml 20 x SSC + 16 ml EDTA, V_f=4L).

F. Oligonucleotides

[0352] *In situ* analysis was performed on a variety of DNA sequences disclosed herein. The oligonucleotides employed for these analyses were obtained so as to be complementary to the nucleic acids (or the complements thereof) as shown in the accompanying figures.

G. Results

[0353] *In situ* analysis was performed on a variety of DNA sequences disclosed herein. The results from these analyses are as follows.

DNA219894 (TAT211)

[0354] In one analysis, 12/14 ovarian adenocarcinomas are positive and 8/9 endometrial adenocarcinomas are positive. Normal ovarian stroma is negative as is uterine myometrium. Other normal ovarian and uterine tissues are negative.

[0355] In an independent analysis, 16/27 non small cell lung carcinomas are positive, wherein the signal is moderate or strong.

EXAMPLE 5: Immunohistochemistry Analysis

[0356] Antibodies against certain TAT polypeptides disclosed herein were prepared and immunohistochemistry analysis was performed as follows. Tissue sections were first fixed for 5 minutes in acetone/ethanol (frozen or paraffin-embedded). The sections were then washed in PBS and then blocked with avidin and biotin (Vector kit) for 10 minutes each followed by a wash in PBS. The sections were then blocked with 10% serum for 20 minutes and then blotted to remove the excess. A primary antibody was then added to the sections at a concentration of 10 μ g/ml for 1 hour and then the sections were washed in PBS. A biotinylated secondary antibody (anti-primary antibody) was then added to the sections for 30 minutes and then the sections were washed with PBS. The sections were then exposed to the reagents of the Vector ABC kit for 30 minutes and then the sections were washed in PBS. The sections were then exposed to Diaminobenzidine (Pierce) for 5 minutes and then washed in PBS. The sections were then counterstained with Mayers hematoxylin, covered with a coverslip and visualized. Immunohistochemistry analysis can also be performed as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989 and Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997).

EXAMPLE 6: Verification and Analysis of Differential TAT Polypeptide Expression by GEPIS

[0357] TAT polypeptides which may have been identified as a tumor antigen as described in one or more of the above Examples were analyzed and verified as follows. An expressed sequence tag (EST) DNA database (LIFESEQ[®], Incyte Pharmaceuticals, Palo Alto, CA) was searched and interesting EST sequences were identified by GEPIS. Gene expression profiling *in silico* (GEPIS) is a bioinformatics tool developed at Genentech, Inc. that characterizes genes of interest for new cancer therapeutic targets. GEPIS takes advantage of large amounts of EST sequence and library information to determine gene expression profiles. GEPIS is capable of determining the expression profile of a gene based upon its proportional correlation with the number of its occurrences in EST databases, and it works by integrating the LIFESEQ[®] EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, GEPIS is used to identify and cross-validate novel tumor antigens, although GEPIS can be configured to perform either very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to identify EST sequences from the LIFESEQ[®] database that correlate to expression in a particular tissue or tissues of interest (often a tumor tissue of interest). The EST sequences identified in this initial screen (or consensus sequences obtained from aligning multiple related and overlapping EST sequences obtained from the initial screen) were then subjected to a screen intended to identify the presence of at least one transmembrane domain in the encoded protein. Finally, GEPIS was employed to generate a complete tissue expression profile for the various sequences of interest. Using this type of screening bioinformatics, various TAT polypeptides (and their encoding nucleic acid molecules) were identified as being significantly overexpressed in a particular type of cancer or certain cancers as compared to other cancers and/or normal non-cancerous tissues. The rating of GEPIS hits is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. Molecules whose tissue expression profile as determined by GEPIS evidences high tissue expression and significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues are excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

EXAMPLE 7: Use of TAT as a hybridization probe

[0358] The following method describes use of a nucleotide sequence encoding TAT as a hybridization probe for, i.e., diagnosis of the presence of a tumor in a mammal.

[0359] DNA comprising the coding sequence of full-length or mature TAT as disclosed herein can also be employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of TAT) in human tissue cDNA libraries or human tissue genomic libraries.

[0360] Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled TAT-derived probe to the filters is performed in a solution of 50% formamide, 5xSSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10 % dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1 % SDS at 42°C.

[0361] DNAs having a desired sequence identity with the DNA encoding full-length native sequence TAT can then be identified using standard techniques known in the art.

EXAMPLE 8: Expression of TAT in *E. coli*

[0362] This example illustrates preparation of an unglycosylated form of TAT by recombinant expression in *E. coli*.

[0363] The DNA sequence encoding TAT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the TAT coding region, lambda transcriptional terminator, and an argU gene.

[0364] The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

[0365] Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

[0366] After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized TAT protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

[0367] TAT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding TAT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55 % (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

[0368] *E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

[0369] The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20

mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10 % final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1 % TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

[0370] Fractions containing the desired folded TAT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

[0371] Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 9: Expression of TAT in mammalian cells

[0372] This example illustrates preparation of a potentially glycosylated form of TAT by recombinant expression in mammalian cells.

[0373] The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the TAT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the TAT DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-TAT.

[0374] In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-TAT DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

[0375] Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of TAT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

[0376] In an alternative technique, TAT may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-TAT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed TAT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

[0377] In another embodiment, TAT can be expressed in CHO cells. The pRK5-TAT can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of TAT polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed TAT can then be concentrated and purified by any selected method.

[0378] Epitope-tagged TAT may also be expressed in host CHO cells. The TAT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged TAT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described

above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged TAT can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

[0379] TAT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

[0380] Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

[0381] Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

[0382] Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Quiagen), Dosper® or Eugene® (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately 3 x 10⁷ cells are frozen in an ampule for further growth and production as described below.

[0383] The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 µm filtered PS20 with 5 % 0.2 µm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 10⁵ cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10⁶ cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 µm filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

[0384] For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

[0385] Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 µL of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

[0386] Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 10: Expression of TAT in Yeast

[0387] The following method describes recombinant expression of TAT in yeast.

[0388] First, yeast expression vectors are constructed for intracellular production or secretion of TAT from the ADH2/GAPDH promoter. DNA encoding TAT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of TAT. For secretion, DNA encoding TAT can be cloned into the

selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native TAT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of TAT.

[0389] Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

[0390] Recombinant TAT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing TAT may further be purified using selected column chromatography resins.

[0391] Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 11: Expression of TAT in Baculovirus-Infected Insect Cells

[0392] The following method describes recombinant expression of TAT in Baculovirus-infected insect cells.

[0393] The sequence coding for TAT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding TAT or the desired portion of the coding sequence of TAT such as the sequence encoding an extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

[0394] Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., *Baculovirus expression vectors: A Laboratory Manual*, Oxford: Oxford University Press (1994).

[0395] Expressed poly-his tagged TAT can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., *Nature*, 362: 175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged TAT are pooled and dialyzed against loading buffer.

[0396] Alternatively, purification of the IgG tagged (or Fc tagged) TAT can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

[0397] Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 12: Preparation of Antibodies that Bind TAT

[0398] This example illustrates preparation of monoclonal antibodies which can specifically bind TAT.

[0399] Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified TAT, fusion proteins containing TAT, and cells expressing recombinant TAT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

[0400] Mice, such as Balb/c, are immunized with the TAT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected

adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-TAT antibodies.

[0401] After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of TAT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35 % polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

[0402] The hybridoma cells will be screened in an ELISA for reactivity against TAT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against TAT is within the skill in the art.

[0403] The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-TAT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

[0404] Antibodies directed against certain of the TAT polypeptides disclosed herein have been successfully produced using this technique(s). More specifically, functional monoclonal antibodies that are capable of recognizing and binding to TAT protein (as measured by standard ELISA, FACS sorting analysis and/or immunohistochemistry analysis) have been successfully generated against the following TAT proteins

TAT110 (DNA95930), TAT210 (DNA95930-1), TAT113 (DNA215609), TAT126 (DNA226539), TAT151 (DNA236511), TAT111 (DNA188221), TAT146 (DNA233876), TAT112 (DNA96930), TAT145 (DNA98565), TAT152 (DNA246435), TAT141 (DNA236493), TAT114 (DNA108809), TAT104 (DNA236343), TAT100 (DNA231542), TAT284 (DNA231542-1), TAT285 (DNA231542-2), TAT285-1 (DNA297393), TAT144 (DNA226456), TAT188 (DNA237637), TAT123 (DNA210499), TAT211 (DNA219894), TAT102 (DNA236534), TAT127 (DNA228199) and TAT128 (DNA220432). Interestingly, Applicants have identified that the monoclonal antibodies prepared against TAT111 (DNA188221) and TAT146 (DNA233876) are capable of blocking activation of the EphB2R receptor encoded by the DNA188221 and DNA233876 molecules by its associated ligand polypeptide. As such, antibodies and methods for using those antibodies for blocking activation of the EphB2R receptor (i.e., TAT111 and TAT146 polypeptides) by its associated ligand are encompassed within the presently described invention. Moreover, Applicants have identified that monoclonal antibodies directed against the TAT110 (DNA95930) and TAT210 (DNA95930-1) polypeptides (i.e., IL-20 receptor alpha polypeptides) are capable of inhibiting activation of the IL20 receptor alpha by IL-19 protein. As such, antibodies and methods for using those antibodies for inhibiting activation of the IL-20 receptor alpha (i.e., TAT110 and TAT210 polypeptides) by IL-19 are encompassed within the presently described invention.

[0405] In addition to the successful preparation of monoclonal antibodies directed against the TAT polypeptides as described herein, many of those monoclonal antibodies have been successfully conjugated to a cell toxin for use in directing the cellular toxin to a cell (or tissue) that expresses a TAT polypeptide of interest (both *in vitro* and *in vivo*). For example, toxin (e.g., DM1) derivitized monoclonal antibodies have been successfully generated to the following TAT polypeptides as described herein: TAT110 (DNA95930), TAT210 (DNA95930-1), TAT112 (DNA96930), TAT113 (DNA215609), TAT111 (DNA188221) and TAT146 (DNA233876).

EXAMPLE 13: Purification of TAT Polypeptides Using Specific Antibodies

[0406] Native or recombinant TAT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-TAT polypeptide, mature TAT polypeptide, or pre-TAT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the TAT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-TAT polypeptide antibody to an activated chromatographic resin.

[0407] Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

[0408] Such an immunoaffinity column is utilized in the purification of TAT polypeptide by preparing a fraction from cells containing TAT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a

subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble TAT polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

[0409] A soluble TAT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TAT polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/TAT polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and TAT polypeptide is collected.

EXAMPLE 14: *In Vitro* Tumor Cell Killing Assay

[0410] Mammalian cells expressing the TAT polypeptide of interest may be obtained using standard expression vector and cloning techniques. Alternatively, many tumor cell lines expressing TAT polypeptides of interest are publicly available, for example, through the ATCC and can be routinely identified using standard ELISA or FACS analysis. Anti-TAT polypeptide monoclonal antibodies (and toxin conjugated derivatives thereof) may then be employed in assays to determine the ability of the antibody to kill TAT polypeptide expressing cells *in vitro*.

[0411] For example, cells expressing the TAT polypeptide of interest are obtained as described above and plated into 96 well dishes. In one analysis, the antibody/toxin conjugate (or naked antibody) is included throughout the cell incubation for a period of 4 days. In a second independent analysis, the cells are incubated for 1 hour with the antibody/toxin conjugate (or naked antibody) and then washed and incubated in the absence of antibody/toxin conjugate for a period of 4 days. Cell viability is then measured using the CellTiter-Glo Luminescent Cell Viability Assay from Promega (Cat# G7571): Untreated cells serve as a negative control.

[0412] In one specific analysis, the ability of monoclonal antibodies directed against TAT112 (DNA96930) were analyzed for the ability to kill cells expressing that polypeptide. In one analysis, an expression vector called gD.NCA was prepared. The TAT112 polypeptide encoding sequences inserted into that vector are driven by an SV40 promoter and the vector also contains the SV40 early poly A signal. The gD.NCA vector was co-transfected into PC3 cells along with an SV40 vector that expresses Neo resistance in PC3 cells, and positive transformants were selected in 800 μ g/ml G418. Positive clones were isolated in 96 well plates and analyzed by flow cytometry using an anti-TAT112 monoclonal antibody prepared as described above and called 3E6. Clone 3 was selected for the analysis as it was found to express a high level of TAT112 polypeptide on its surface. In a second independent analysis, the pancreatic cancer cell line, HpaF II, was obtained from the ATCC and employed in the assay.

[0413] The results from the above described assay demonstrated that DM1-conjugated anti-TAT112 monoclonal antibodies were highly efficacious in killing both the TAT112 expressing PC3 cell line as well as the pancreatic cancer cell line HpaF II as compared to the untreated negative controls.

EXAMPLE 15: *In Vivo* Tumor Cell Killing Assay

[0414] To test the efficacy of unconjugated anti-TAT112 monoclonal antibodies, anti-TAT112 antibody was injected intraperitoneally into nude mice 24 hours prior to receiving PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) subcutaneously in the flank. Antibody injections continued twice per week for the remainder of the study. Tumor volume was measured twice per week.

[0415] To test the efficacy of DM1-conjugated anti-TAT112 antibody, PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) were inoculated into the flank of nude mice. When the tumors reached a mean volume of approximately 100mm³, mice were treated with DM1-conjugated anti-TAT112 antibody intravenously either once or twice per week.

[0416] The results of the above analyses demonstrated that both the unconjugated anti-TAT112 as well as the DM1-conjugated anti-TAT112 antibody were highly efficacious in reducing tumor volume in this *in vivo* model. These analyses demonstrate that anti-TAT polypeptide monoclonal antibodies are efficacious for killing tumor cells that express a TAT polypeptide of interest.

EXAMPLE 16: Northern Blot Analysis

[0417] Northern blot analysis was performed essentially as described by Sambrook et al., *supra*. Northern blot analysis using probes derived from DNA231542, DNA231542-1, DNA231542-2 and DNA297393 evidences significant upregulation of expression in human glioma tissue as compared to normal human brain tissue.

[0418] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent

are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

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5 Gln Phe Gln Phe Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile
 65 70 75
 Pro Ala Pro Thr Pro Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr
 80 85 90
 10 Glu Pro Gly Pro Leu Asp Cys Arg Glu Glu Gln Tyr Pro Cys Thr
 95 100 105
 Arg Leu Tyr Ser Ile His Arg Pro Cys Lys Gln Cys Leu Asn Glu
 110 115 120
 15 Val Cys Phe Tyr Ser Leu Arg Arg Val Tyr Val Ile Asn Lys Glu
 125 130 135
 Ile Cys Val Arg Thr Val Cys Ala His Glu Glu Leu Leu Arg Ala
 140 145 150
 20 Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys Gly Val Met Ala Ser
 155 160 165
 Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys Ala Arg Ser Cys
 170 175 180
 25 Gly Ser Cys
 <210> 80
 <211> 909
 <212> PRT
 30 <213> Homo Sapien
 <400> 80
 Met Ala Ala Arg Pro Leu Pro Val Ser Pro Ala Arg Ala Leu Leu
 1 5 10 15
 35 Leu Ala Leu Ala Gly Ala Leu Leu Ala Pro Cys Glu Ala Arg Gly
 20 25 30
 Val Ser Leu Trp Asn Glu Gly Arg Ala Asp Glu Val Val Ser Ala
 35 40 45
 40 Ser Val Arg Ser Gly Asp Leu Trp Ile Pro Val Lys Ser Phe Asp
 50 55 60
 Ser Lys Asn His Pro Glu Val Leu Asn Ile Arg Leu Gln Arg Glu
 65 70 75
 45 Ser Lys Glu Leu Ile Ile Asn Leu Glu Arg Asn Glu Gly Leu Ile
 80 85 90
 Ala Ser Ser Phe Thr Glu Thr His Tyr Leu Gln Asp Gly Thr Asp
 95 100 105
 50 Val Ser Leu Ala Arg Asn Tyr Thr Val Ile Leu Gly His Cys Tyr
 110 115 120
 Tyr His Gly His Val Arg Gly Tyr Ser Asp Ser Ala Val Ser Leu
 125 130 135
 55

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	Ser	Thr	Cys	Ser	Gly	Leu	Arg	Gly	Leu	Ile	Val	Phe	Glu	Asn	Glu
					140					145					150
5	Ser	Tyr	Val	Leu	Glu	Pro	Met	Lys	Ser	Ala	Thr	Asn	Arg	Tyr	Lys
					155					160					165
	Leu	Phe	Pro	Ala	Lys	Lys	Leu	Lys	Ser	Val	Arg	Gly	Ser	Cys	Gly
					170					175					180
10	Ser	His	His	Asn	Thr	Pro	Asn	Leu	Ala	Ala	Lys	Asn	Val	Phe	Pro
					185					190					195
	Pro	Pro	Ser	Gln	Thr	Trp	Ala	Arg	Arg	His	Lys	Arg	Glu	Thr	Leu
					200					205					210
15	Lys	Ala	Thr	Lys	Tyr	Val	Glu	Leu	Val	Ile	Val	Ala	Asp	Asn	Arg
					215					220					225
	Glu	Phe	Gln	Arg	Gln	Gly	Lys	Asp	Leu	Glu	Lys	Val	Lys	Gln	Arg
					230					235					240
20	Leu	Ile	Glu	Ile	Ala	Asn	His	Val	Asp	Lys	Phe	Tyr	Arg	Pro	Leu
					245					250					255
	Asn	Ile	Arg	Ile	Val	Leu	Val	Gly	Val	Glu	Val	Trp	Asn	Asp	Met
25					260					265					270
	Asp	Lys	Cys	Ser	Val	Ser	Gln	Asp	Pro	Phe	Thr	Ser	Leu	His	Glu
					275					280					285
30	Phe	Leu	Asp	Trp	Arg	Lys	Met	Lys	Leu	Leu	Pro	Arg	Lys	Ser	His
					290					295					300
	Asp	Asn	Ala	Gln	Leu	Val	Ser	Gly	Val	Tyr	Phe	Gln	Gly	Thr	Thr
					305					310					315
35	Ile	Gly	Met	Ala	Pro	Ile	Met	Ser	Met	Cys	Thr	Ala	Asp	Gln	Ser
					320					325					330
	Gly	Gly	Ile	Val	Met	Asp	His	Ser	Asp	Asn	Pro	Leu	Gly	Ala	Ala
					335					340					345
40	Val	Thr	Leu	Ala	His	Glu	Leu	Gly	His	Asn	Phe	Gly	Met	Asn	His
					350					355					360
	Asp	Thr	Leu	Asp	Arg	Gly	Cys	Ser	Cys	Gln	Met	Ala	Val	Glu	Lys
					365					370					375
45	Gly	Gly	Cys	Ile	Met	Asn	Ala	Ser	Thr	Gly	Tyr	Pro	Phe	Pro	Met
					380					385					390
	Val	Phe	Ser	Ser	Cys	Ser	Arg	Lys	Asp	Leu	Glu	Thr	Ser	Leu	Glu
					395					400					405
50	Lys	Gly	Met	Gly	Val	Cys	Leu	Phe	Asn	Leu	Pro	Glu	Val	Arg	Glu
					410					415					420
	Ser	Phe	Gly	Gly	Gln	Lys	Cys	Gly	Asn	Arg	Phe	Val	Glu	Glu	Gly
					425					430					435
55	Glu	Glu	Cys	Asp	Cys	Gly	Glu	Pro	Glu	Glu	Cys	Met	Asn	Arg	Cys

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					440					445					450	
5		Cys	Asn	Ala	Thr	Thr	Cys	Thr	Leu	Lys	Pro	Asp	Ala	Val	Cys	Ala
					455						460					465
		His	Gly	Leu	Cys	Cys	Glu	Asp	Cys	Gln	Leu	Lys	Pro	Ala	Gly	Thr
					470						475					480
10		Ala	Cys	Arg	Asp	Ser	Ser	Asn	Ser	Cys	Asp	Leu	Pro	Glu	Phe	Cys
					485						490					495
		Thr	Gly	Ala	Ser	Pro	His	Cys	Pro	Ala	Asn	Val	Tyr	Leu	His	Asp
					500						505					510
15		Gly	His	Ser	Cys	Gln	Asp	Val	Asp	Gly	Tyr	Cys	Tyr	Asn	Gly	Ile
					515						520					525
		Cys	Gln	Thr	His	Glu	Gln	Gln	Cys	Val	Thr	Leu	Trp	Gly	Pro	Gly
					530						535					540
20		Ala	Lys	Pro	Ala	Pro	Gly	Ile	Cys	Phe	Glu	Arg	Val	Asn	Ser	Ala
					545						550					555
		Gly	Asp	Pro	Tyr	Gly	Asn	Cys	Gly	Lys	Val	Ser	Lys	Ser	Ser	Phe
					560						565					570
25		Ala	Lys	Cys	Glu	Met	Arg	Asp	Ala	Lys	Cys	Gly	Lys	Ile	Gln	Cys
					575						580					585
		Gln	Gly	Gly	Ala	Ser	Arg	Pro	Val	Ile	Gly	Thr	Asn	Ala	Val	Ser
					590						595					600
30		Ile	Glu	Thr	Asn	Ile	Pro	Leu	Gln	Gln	Gly	Gly	Arg	Ile	Leu	Cys
					605						610					615
		Arg	Gly	Thr	His	Val	Tyr	Leu	Gly	Asp	Asp	Met	Pro	Asp	Pro	Gly
					620						625					630
35		Leu	Val	Leu	Ala	Gly	Thr	Lys	Cys	Ala	Asp	Gly	Lys	Ile	Cys	Leu
					635						640					645
		Asn	Arg	Gln	Cys	Gln	Asn	Ile	Ser	Val	Phe	Gly	Val	His	Glu	Cys
					650						655					660
40		Ala	Met	Gln	Cys	His	Gly	Arg	Gly	Val	Cys	Asn	Asn	Arg	Lys	Asn
					665						670					675
		Cys	His	Cys	Glu	Ala	His	Trp	Ala	Pro	Pro	Phe	Cys	Asp	Lys	Phe
					680						685					690
45		Gly	Phe	Gly	Gly	Ser	Thr	Asp	Ser	Gly	Pro	Ile	Arg	Gln	Ala	Asp
					695						700					705
		Asn	Gln	Gly	Leu	Thr	Ile	Gly	Ile	Leu	Val	Thr	Ile	Leu	Cys	Leu
					710						715					720
50		Leu	Ala	Ala	Gly	Phe	Val	Val	Tyr	Leu	Lys	Arg	Lys	Thr	Leu	Ile
					725						730					735
		Arg	Leu	Leu	Phe	Thr	Asn	Lys	Lys	Thr	Thr	Ile	Glu	Lys	Leu	Arg
55					740						745					750

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5 Cys Val Arg Pro Ser Arg Pro Pro Arg Gly Phe Gln Pro Cys Gln
 755 760 765
 Ala His Leu Gly His Leu Gly Lys Gly Leu Met Arg Lys Pro Pro
 770 775 780
 10 Asp Ser Tyr Pro Pro Lys Asp Asn Pro Arg Arg Leu Leu Gln Cys
 785 790 795
 Gln Asn Val Asp Ile Ser Arg Pro Leu Asn Gly Leu Asn Val Pro
 800 805 810
 15 Gln Pro Gln Ser Thr Gln Arg Val Leu Pro Pro Leu His Arg Ala
 815 820 825
 Pro Arg Ala Pro Ser Val Pro Ala Arg Pro Leu Pro Ala Lys Pro
 830 835 840
 20 Ala Leu Arg Gln Ala Gln Gly Thr Cys Lys Pro Asn Pro Pro Gln
 845 850 855
 Lys Pro Leu Pro Ala Asp Pro Leu Ala Arg Thr Thr Arg Leu Thr
 860 865 870
 25 His Ala Leu Ala Arg Thr Pro Gly Gln Trp Glu Thr Gly Leu Arg
 875 880 885
 Leu Ala Pro Leu Arg Pro Ala Pro Gln Tyr Pro His Gln Val Pro
 890 895 900
 30 Arg Ser Thr His Thr Ala Tyr Ile Lys
 905
 <210> 81
 <211> 158
 <212> PRT
 35 <213> Homo Sapien
 <400> 81
 Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu
 1 5 10 15
 40 Ala Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys
 20 25 30
 Ala Pro Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe
 35 40 45
 45 Arg Lys Leu Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser
 50 55 60
 Tyr Gly Asn Gly Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu
 65 70 75
 50 Ala Ser Thr Ile Ala Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln
 80 85 90
 Pro Ile Trp Ile Gly Leu His Asp Pro Gln Lys Arg Gln Gln Trp
 95 100 105
 55

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Gln Trp Ile Asp Gly Ala Met Tyr Leu Tyr Arg Ser Trp Ser Gly
110 115 120

5 Lys Ser Met Gly Gly Asn Lys His Cys Ala Glu Ile Ser Ser Asn
125 130 135

Asn Asn Phe Leu Thr Trp Ser Ser Asn Glu Cys Asn Lys Arg Gln
140 145 150

10 His Phe Leu Cys Lys Tyr Arg Pro
155

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<211> 84
15 <212> PRT
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<400> 82
Met Ala Thr Met Glu Asn Lys Val Ile Cys Ala Leu Val Leu Val
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20 Ser Met Leu Ala Leu Gly Thr Leu Ala Glu Ala Gln Thr Glu Thr
20 25 30

Cys Thr Val Ala Pro Arg Glu Arg Gln Asn Cys Gly Phe Pro Gly
35 40 45

25 Val Thr Pro Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe Asp Asp
50 55 60

Thr Val Arg Gly Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile Asp
65 70 75

30 Val Pro Pro Glu Glu Glu Cys Glu Phe
80

<210> 83
35 <211> 680
<212> PRT
<213> Homo Sapien

<400> 83
Met Leu Pro Gln Ile Pro Phe Leu Leu Leu Val Ser Leu Asn Leu
1 5 10 15

Val His Gly Val Phe Tyr Ala Glu Arg Tyr Gln Thr Pro Thr Gly
20 25 30

45 Ile Lys Gly Pro Leu Pro Asn Thr Lys Thr Gln Phe Phe Ile Pro
35 40 45

Tyr Thr Ile Lys Ser Lys Gly Ile Ala Val Arg Gly Glu Gln Gly
50 55 60

Thr Pro Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly His Pro Gly
65 70 75

Pro Ser Gly Pro Pro Gly Lys Pro Gly Tyr Gly Ser Pro Gly Leu
80 85 90

55 Gln Gly Glu Pro Gly Leu Pro Gly Pro Pro Gly Pro Ser Ala Val

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	95	100	105
5	Gly Lys Pro Gly Val Pro Gly Leu Pro Gly Lys Pro Gly Glu Arg 110 115 120		
	Gly Pro Tyr Gly Pro Lys Gly Asp Val Gly Pro Ala Gly Leu Pro 125 130 135		
10	Gly Pro Arg Gly Pro Pro Gly Pro Pro Gly Ile Pro Gly Pro Ala 140 145 150		
	Gly Ile Ser Val Pro Gly Lys Pro Gly Gln Gln Gly Pro Thr Gly 155 160 165		
15	Ala Pro Gly Pro Arg Gly Phe Pro Gly Glu Lys Gly Ala Pro Gly 170 175 180		
	Val Pro Gly Met Asn Gly Gln Lys Gly Glu Met Gly Tyr Gly Ala 185 190 195		
20	Pro Gly Arg Pro Gly Glu Arg Gly Leu Pro Gly Pro Gln Gly Pro 200 205 210		
	Thr Gly Pro Ser Gly Pro Pro Gly Val Gly Lys Arg Gly Glu Asn 215 220 225		
25	Gly Val Pro Gly Gln Pro Gly Ile Lys Gly Asp Arg Gly Phe Pro 230 235 240		
	Gly Glu Met Gly Pro Ile Gly Pro Pro Gly Pro Gln Gly Pro Pro 245 250 255		
30	Gly Glu Arg Gly Pro Glu Gly Ile Gly Lys Pro Gly Ala Ala Gly 260 265 270		
	Ala Pro Gly Gln Pro Gly Ile Pro Gly Thr Lys Gly Leu Pro Gly 275 280 285		
35	Ala Pro Gly Ile Ala Gly Pro Pro Gly Pro Pro Gly Phe Gly Lys 290 295 300		
	Pro Gly Leu Pro Gly Leu Lys Gly Glu Arg Gly Pro Ala Gly Leu 305 310 315		
40	Pro Gly Gly Pro Gly Ala Lys Gly Glu Gln Gly Pro Ala Gly Leu 320 325 330		
	Pro Gly Lys Pro Gly Leu Thr Gly Pro Pro Gly Asn Met Gly Pro 335 340 345		
45	Gln Gly Pro Lys Gly Ile Pro Gly Ser His Gly Leu Pro Gly Pro 350 355 360		
	Lys Gly Glu Thr Gly Pro Ala Gly Pro Ala Gly Tyr Pro Gly Ala 365 370 375		
50	Lys Gly Glu Arg Gly Ser Pro Gly Ser Asp Gly Lys Pro Gly Tyr 380 385 390		
55	Pro Gly Lys Pro Gly Leu Asp Gly Pro Lys Gly Asn Pro Gly Leu 395 400 405		

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5	Pro Gly Pro Lys Gly Asp Pro Gly Val Gly Gly Pro Pro Gly Leu	410	415	420
	Pro Gly Pro Val Gly Pro Ala Gly Ala Lys Gly Met Pro Gly His	425	430	435
10	Asn Gly Glu Ala Gly Pro Arg Gly Ala Pro Gly Ile Pro Gly Thr	440	445	450
	Arg Gly Pro Ile Gly Pro Pro Gly Ile Pro Gly Phe Pro Gly Ser	455	460	465
15	Lys Gly Asp Pro Gly Ser Pro Gly Pro Pro Gly Pro Ala Gly Ile	470	475	480
	Ala Thr Lys Gly Leu Asn Gly Pro Thr Gly Pro Pro Gly Pro Pro	485	490	495
20	Gly Pro Arg Gly Pro Ser Gly Glu Pro Gly Leu Pro Gly Pro Pro	500	505	510
	Gly Pro Pro Gly Pro Pro Gly Gln Ala Val Met Pro Glu Gly Phe	515	520	525
25	Ile Lys Ala Gly Gln Arg Pro Ser Leu Ser Gly Thr Pro Leu Val	530	535	540
	Ser Ala Asn Gln Gly Val Thr Gly Met Pro Val Ser Ala Phe Thr	545	550	555
30	Val Ile Leu Ser Lys Ala Tyr Pro Ala Ile Gly Thr Pro Ile Pro	560	565	570
	Phe Asp Lys Ile Leu Tyr Asn Arg Gln Gln His Tyr Asp Pro Arg	575	580	585
35	Thr Gly Ile Phe Thr Cys Gln Ile Pro Gly Ile Tyr Tyr Phe Ser	590	595	600
	Tyr His Val His Val Lys Gly Thr His Val Trp Val Gly Leu Tyr	605	610	615
40	Lys Asn Gly Thr Pro Val Met Tyr Thr Tyr Asp Glu Tyr Thr Lys	620	625	630
	Gly Tyr Leu Asp Gln Ala Ser Gly Ser Ala Ile Ile Asp Leu Thr	635	640	645
45	Glu Asn Asp Gln Val Trp Leu Gln Leu Pro Asn Ala Glu Ser Asn	650	655	660
	Gly Leu Tyr Ser Ser Glu Tyr Val His Ser Ser Phe Ser Gly Phe	665	670	675
50	Leu Val Ala Pro Met	680		
55	<210> 84			
	<211> 542			
	<212> PRT			

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<213> Homo Sapien

<400> 84

5	Met	Pro	Leu	Pro	Pro	Leu	Leu	Leu	Leu	Leu	Leu	Ala	Ala	Pro	Trp	1	5	10	15
	Gly	Arg	Ala	Val	Pro	Cys	Val	Ser	Gly	Gly	Leu	Pro	Lys	Pro	Ala	20	25	30	
10	Asn	Ile	Thr	Phe	Leu	Ser	Ile	Asn	Met	Lys	Asn	Val	Leu	Gln	Trp	35	40	45	
	Thr	Pro	Pro	Glu	Gly	Leu	Gln	Gly	Val	Lys	Val	Thr	Tyr	Thr	Val	50	55	60	
15	Gln	Tyr	Phe	Ile	Tyr	Gly	Gln	Lys	Lys	Trp	Leu	Asn	Lys	Ser	Glu	65	70	75	
	Cys	Arg	Asn	Ile	Asn	Arg	Thr	Tyr	Cys	Asp	Leu	Ser	Ala	Glu	Thr	80	85	90	
20	Ser	Asp	Tyr	Glu	His	Gln	Tyr	Tyr	Ala	Lys	Val	Lys	Ala	Ile	Trp	95	100	105	
	Gly	Thr	Lys	Cys	Ser	Lys	Trp	Ala	Glu	Ser	Gly	Arg	Phe	Tyr	Pro	110	115	120	
25	Phe	Leu	Glu	Thr	Gln	Ile	Gly	Pro	Pro	Glu	Val	Ala	Leu	Thr	Thr	125	130	135	
	Asp	Glu	Lys	Ser	Ile	Ser	Val	Val	Leu	Thr	Ala	Pro	Glu	Lys	Trp	140	145	150	
30	Lys	Arg	Asn	Pro	Glu	Asp	Leu	Pro	Val	Ser	Met	Gln	Gln	Ile	Tyr	155	160	165	
	Ser	Asn	Leu	Lys	Tyr	Asn	Val	Ser	Val	Leu	Asn	Thr	Lys	Ser	Asn	170	175	180	
35	Arg	Thr	Trp	Ser	Gln	Cys	Val	Thr	Asn	His	Thr	Leu	Val	Leu	Thr	185	190	195	
	Trp	Leu	Glu	Pro	Asn	Thr	Leu	Tyr	Cys	Val	His	Val	Glu	Ser	Phe	200	205	210	
40	Val	Pro	Gly	Pro	Pro	Arg	Arg	Ala	Gln	Pro	Ser	Glu	Lys	Gln	Cys	215	220	225	
	Ala	Arg	Thr	Leu	Lys	Asp	Gln	Ser	Ser	Glu	Phe	Lys	Ala	Lys	Ile	230	235	240	
45	Ile	Phe	Trp	Tyr	Val	Leu	Pro	Ile	Ser	Ile	Thr	Val	Phe	Leu	Phe	245	250	255	
	Ser	Val	Met	Gly	Tyr	Ser	Ile	Tyr	Arg	Tyr	Ile	His	Val	Gly	Lys	260	265	270	
50	Glu	Lys	His	Pro	Ala	Asn	Leu	Ile	Leu	Ile	Tyr	Gly	Asn	Glu	Phe	275	280	285	
55	Asp	Lys	Arg	Phe	Phe	Val	Pro	Ala	Glu	Lys	Ile	Val	Ile	Asn	Phe				

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				290					295					300	
5	Ile	Thr	Leu	Asn	Ile	Ser	Asp	Asp	Ser	Lys	Ile	Ser	His	Gln	Asp
				305						310				315	
	Met	Ser	Leu	Leu	Gly	Lys	Ser	Ser	Asp	Val	Ser	Ser	Leu	Asn	Asp
				320						325				330	
10	Pro	Gln	Pro	Ser	Gly	Asn	Leu	Arg	Pro	Pro	Gln	Glu	Glu	Glu	Glu
					335					340				345	
	Val	Lys	His	Leu	Gly	Tyr	Ala	Ser	His	Leu	Met	Glu	Ile	Phe	Cys
					350					355				360	
15	Asp	Ser	Glu	Glu	Asn	Thr	Glu	Gly	Thr	Ser	Leu	Thr	Gln	Gln	Glu
					365					370				375	
	Ser	Leu	Ser	Arg	Thr	Ile	Pro	Pro	Asp	Lys	Thr	Val	Ile	Glu	Tyr
					380					385				390	
20	Glu	Tyr	Asp	Val	Arg	Thr	Thr	Asp	Ile	Cys	Ala	Gly	Pro	Glu	Glu
					395					400				405	
	Gln	Glu	Leu	Ser	Leu	Gln	Glu	Glu	Val	Ser	Thr	Gln	Gly	Thr	Leu
					410					415				420	
25	Leu	Glu	Ser	Gln	Ala	Ala	Leu	Ala	Val	Leu	Gly	Pro	Gln	Thr	Leu
					425					430				435	
	Gln	Tyr	Ser	Tyr	Thr	Pro	Gln	Leu	Gln	Asp	Leu	Asp	Pro	Leu	Ala
					440					445				450	
30	Gln	Glu	His	Thr	Asp	Ser	Glu	Glu	Gly	Pro	Glu	Glu	Glu	Pro	Ser
					455					460				465	
	Thr	Thr	Leu	Val	Asp	Trp	Asp	Pro	Gln	Thr	Gly	Arg	Leu	Cys	Ile
					470					475				480	
35	Pro	Ser	Leu	Ser	Ser	Phe	Asp	Gln	Asp	Ser	Glu	Gly	Cys	Glu	Pro
					485					490				495	
	Ser	Glu	Gly	Asp	Gly	Leu	Gly	Glu	Glu	Gly	Leu	Leu	Ser	Arg	Leu
					500					505				510	
40	Tyr	Glu	Glu	Pro	Ala	Pro	Asp	Arg	Pro	Pro	Gly	Glu	Asn	Glu	Thr
					515					520				525	
	Tyr	Leu	Met	Gln	Phe	Met	Glu	Glu	Trp	Gly	Leu	Tyr	Val	Gln	Met
					530					535				540	
45															
	Glu	Asn													
50	<210>	85													
	<211>	553													
	<212>	PRT													
	<213>	Homo Sapien													
	<400>	85													
55	Met	Arg	Ala	Pro	Gly	Arg	Pro	Ala	Leu	Arg	Pro	Leu	Pro	Leu	Pro
	1				5					10				15	

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5	Pro Leu Leu Leu Leu Leu Leu Ala Ala Pro Trp Gly Arg Ala Val	20	25	30
	Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe	35	40	45
10	Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu	50	55	60
	Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile	65	70	75
15	Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile	80	85	90
	Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu	95	100	105
20	His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys	110	115	120
	Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr	125	130	135
25	Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser	140	145	150
	Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro	155	160	165
30	Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys	170	175	180
	Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser	185	190	195
35	Gln Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro	200	205	210
	Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro	215	220	225
40	Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu	230	235	240
	Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys Ile Ile Phe Trp Tyr	245	250	255
45	Val Leu Pro Ile Ser Ile Thr Val Phe Leu Phe Ser Val Met Gly	260	265	270
	Tyr Ser Ile Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro	275	280	285
50	Ala Asn Leu Ile Leu Ile Tyr Gly Asn Glu Phe Asp Lys Arg Phe	290	295	300
	Phe Val Pro Ala Glu Lys Ile Val Ile Asn Phe Ile Thr Leu Asn	305	310	315
55				

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	Ile Ser Asp Asp Ser Lys Ile Ser His Gln Asp Met Ser Leu Leu	320	325	330
5	Gly Lys Ser Ser Asp Val Ser Ser Leu Asn Asp Pro Gln Pro Ser	335	340	345
	Gly Asn Leu Arg Pro Pro Gln Glu Glu Glu Glu Val Lys His Leu	350	355	360
10	Gly Tyr Ala Ser His Leu Met Glu Ile Phe Cys Asp Ser Glu Glu	365	370	375
	Asn Thr Glu Gly Thr Ser Leu Thr Gln Gln Glu Ser Leu Ser Arg	380	385	390
15	Thr Ile Pro Pro Asp Lys Thr Val Ile Glu Tyr Glu Tyr Asp Val	395	400	405
	Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu Gln Glu Leu Ser	410	415	420
20	Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu Glu Ser Gln	425	430	435
	Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr Ser Tyr	440	445	450
25	Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His Thr	455	460	465
	Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val	470	475	480
30	Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser	485	490	495
	Ser Phe Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp	500	505	510
35	Gly Leu Gly Glu Glu Gly Leu Leu Ser Arg Leu Tyr Glu Glu Pro	515	520	525
	Ala Pro Asp Arg Pro Pro Gly Glu Asn Glu Thr Tyr Leu Met Gln	530	535	540
40	Phe Met Glu Glu Trp Gly Leu Tyr Val Gln Met Glu Asn	545	550	
45	<210> 86			
	<211> 95			
	<212> PRT			
	<213> Homo Sapien			
	<400> 86			
50	Met Ala Ala Ala Arg Leu Cys Leu Ser Leu Leu Leu Leu Ser Thr	1	5	10 15
	Cys Val Ala Leu Leu Leu Gln Pro Leu Leu Gly Ala Gln Gly Ala	20	25	30
55	Pro Leu Glu Pro Val Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln			

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					35					40				45	
5	Met	Ala	Gln	Tyr	Ala	Ala	Asp	Leu	Arg	Arg	Tyr	Ile	Asn	Met	Leu
					50					55				60	
	Thr	Arg	Pro	Arg	Tyr	Gly	Lys	Arg	His	Lys	Glu	Asp	Thr	Leu	Ala
					65					70				75	
10	Phe	Ser	Glu	Trp	Gly	Ser	Pro	His	Ala	Ala	Val	Pro	Arg	Glu	Leu
					80					85				90	
	Ser	Pro	Leu	Asp	Leu										
					95										
15	<210> 87														
	<211> 344														
	<212> PRT														
	<213> Homo Sapien														
	<400> 87														
20	Met	Gly	Pro	Pro	Ser	Ala	Pro	Pro	Cys	Arg	Leu	His	Val	Pro	Trp
	1				5					10					15
	Lys	Glu	Val	Leu	Leu	Thr	Ala	Ser	Leu	Leu	Thr	Phe	Trp	Asn	Pro
					20					25					30
25	Pro	Thr	Thr	Ala	Lys	Leu	Thr	Ile	Glu	Ser	Thr	Pro	Phe	Asn	Val
					35					40					45
	Ala	Glu	Gly	Lys	Glu	Val	Leu	Leu	Leu	Ala	His	Asn	Leu	Pro	Gln
					50					55					60
30	Asn	Arg	Ile	Gly	Tyr	Ser	Trp	Tyr	Lys	Gly	Glu	Arg	Val	Asp	Gly
					65					70					75
	Asn	Ser	Leu	Ile	Val	Gly	Tyr	Val	Ile	Gly	Thr	Gln	Gln	Ala	Thr
					80					85					90
35	Pro	Gly	Pro	Ala	Tyr	Ser	Gly	Arg	Glu	Thr	Ile	Tyr	Pro	Asn	Ala
					95					100					105
	Ser	Leu	Leu	Ile	Gln	Asn	Val	Thr	Gln	Asn	Asp	Thr	Gly	Phe	Tyr
					110					115					120
40	Thr	Leu	Gln	Val	Ile	Lys	Ser	Asp	Leu	Val	Asn	Glu	Glu	Ala	Thr
					125					130					135
	Gly	Gln	Phe	His	Val	Tyr	Pro	Glu	Leu	Pro	Lys	Pro	Ser	Ile	Ser
					140					145					150
45	Ser	Asn	Asn	Ser	Asn	Pro	Val	Glu	Asp	Lys	Asp	Ala	Val	Ala	Phe
					155					160					165
	Thr	Cys	Glu	Pro	Glu	Val	Gln	Asn	Thr	Thr	Tyr	Leu	Trp	Trp	Val
					170					175					180
50	Asn	Gly	Gln	Ser	Leu	Pro	Val	Ser	Pro	Arg	Leu	Gln	Leu	Ser	Asn
					185					190					195
55	Gly	Asn	Met	Thr	Leu	Thr	Leu	Leu	Ser	Val	Lys	Arg	Asn	Asp	Ala
					200					205					210

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5	Gly Ser Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn Arg	215	220	225
	Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Gly Pro	230	235	240
10	Thr Ile Ser Pro Ser Lys Ala Asn Tyr Arg Pro Gly Glu Asn Leu	245	250	255
	Asn Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser	260	265	270
15	Trp Phe Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe	275	280	285
	Ile Pro Asn Ile Thr Val Asn Asn Ser Gly Ser Tyr Met Cys Gln	290	295	300
20	Ala His Asn Ser Ala Thr Gly Leu Asn Arg Thr Thr Val Thr Met	305	310	315
	Ile Thr Val Ser Gly Ser Ala Pro Val Leu Ser Ala Val Ala Thr	320	325	330
25	Val Gly Ile Thr Ile Gly Val Leu Ala Arg Val Ala Leu Ile	335	340	
30	<210> 88 <211> 987 <212> PRT <213> Homo Sapien			
	<400> 88			
	Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala	1	5	10 15
35	Leu Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu	20	25	30
	Lys Trp Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu	35	40	45
40	Ser Gly Leu Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val	50	55	60
	Cys Asp Val Gln Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr	65	70	75
45	Gly Trp Val Pro Arg Arg Gly Ala Val His Val Tyr Ala Thr Leu	80	85	90
	Arg Phe Thr Met Leu Glu Cys Leu Ser Leu Pro Arg Ala Gly Arg	95	100	105
50	Ser Cys Lys Glu Thr Phe Thr Val Phe Tyr Tyr Glu Ser Asp Ala	110	115	120
55	Asp Thr Ala Thr Ala Leu Thr Pro Ala Trp Met Glu Asn Pro Tyr	125	130	135

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	Ile Lys Val Asp Thr Val Ala Ala Glu His Leu Thr Arg Lys Arg	140	145	150
5	Pro Gly Ala Glu Ala Thr Gly Lys Val Asn Val Lys Thr Leu Arg	155	160	165
	Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala Phe Gln Asp	170	175	180
10	Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu Phe Tyr Lys	185	190	195
	Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro Glu Thr	200	205	210
15	Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val Val	215	220	225
	Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg	230	235	240
20	Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys	245	250	255
	Ala Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala	260	265	270
25	Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys	275	280	285
	Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala	290	295	300
30	Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro	305	310	315
	Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg Ser Val	320	325	330
35	Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser Ala	335	340	345
	Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg	350	355	360
40	Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly	365	370	375
	Asp Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp	380	385	390
45	Val Val Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu	395	400	405
	Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val	410	415	420
50	Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro	425	430	435
55	Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser Ser Leu			

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		440		445		450									
5	Ser	Leu	Ala	Trp	Ala	Val	Pro	Arg	Ala	Pro	Ser	Gly	Ala	Val	Leu
					455					460					465
	Asp	Tyr	Glu	Val	Lys	Tyr	His	Glu	Lys	Gly	Ala	Glu	Gly	Pro	Ser
					470					475					480
10	Ser	Val	Arg	Phe	Leu	Lys	Thr	Ser	Glu	Asn	Arg	Ala	Glu	Leu	Arg
					485					490					495
	Gly	Leu	Lys	Arg	Gly	Ala	Ser	Tyr	Leu	Val	Gln	Val	Arg	Ala	Arg
					500					505					510
15	Ser	Glu	Ala	Gly	Tyr	Gly	Pro	Phe	Gly	Gln	Glu	His	His	Ser	Gln
					515					520					525
	Thr	Gln	Leu	Asp	Glu	Ser	Glu	Gly	Trp	Arg	Glu	Gln	Leu	Ala	Leu
					530					535					540
20	Ile	Ala	Gly	Thr	Ala	Val	Val	Gly	Val	Val	Leu	Val	Leu	Val	Val
					545					550					555
	Ile	Val	Val	Ala	Val	Leu	Cys	Leu	Arg	Lys	Gln	Ser	Asn	Gly	Arg
					560					565					570
25	Glu	Ala	Glu	Tyr	Ser	Asp	Lys	His	Gly	Gln	Tyr	Leu	Ile	Gly	His
					575					580					585
	Gly	Thr	Lys	Val	Tyr	Ile	Asp	Pro	Phe	Thr	Tyr	Glu	Asp	Pro	Asn
					590					595					600
30	Glu	Ala	Val	Arg	Glu	Phe	Ala	Lys	Glu	Ile	Asp	Val	Ser	Tyr	Val
					605					610					615
	Lys	Ile	Glu	Glu	Val	Ile	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Cys
					620					625					630
35	Arg	Gly	Arg	Leu	Lys	Ala	Pro	Gly	Lys	Lys	Glu	Ser	Cys	Val	Ala
					635					640					645
	Ile	Lys	Thr	Leu	Lys	Gly	Gly	Tyr	Thr	Glu	Arg	Gln	Arg	Arg	Glu
					650					655					660
40	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met	Gly	Gln	Phe	Glu	His	Pro	Asn
					665					670					675
	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Asn	Ser	Met	Pro	Val	Met
					680					685					690
45	Ile	Leu	Thr	Glu	Phe	Met	Glu	Asn	Gly	Ala	Leu	Asp	Ser	Phe	Leu
					695					700					705
	Arg	Leu	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln	Leu	Val	Gly	Met
					710					715					720
50	Leu	Arg	Gly	Ile	Ala	Ser	Gly	Met	Arg	Tyr	Leu	Ala	Glu	Met	Ser
					725					730					735
55	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Asn	Ser
					740					745					750

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5	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Phe	Leu	755	760	765
	Glu	Glu	Asn	Ser	Ser	Asp	Pro	Thr	Tyr	Thr	Ser	Ser	Leu	Gly	Gly	770	775	780
10	Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Phe	Arg	785	790	795
	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Ala	Trp	Ser	Tyr	Gly	Ile	Val	Met	800	805	810
15	Trp	Glu	Val	Met	Ser	Phe	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	815	820	825
	Asn	Gln	Asp	Val	Ile	Asn	Ala	Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	830	835	840
20	Pro	Pro	Pro	Asp	Cys	Pro	Thr	Ser	Leu	His	Gln	Leu	Met	Leu	Asp	845	850	855
	Cys	Trp	Gln	Lys	Asp	Arg	Asn	Ala	Arg	Pro	Arg	Phe	Pro	Gln	Val	860	865	870
25	Val	Ser	Ala	Leu	Asp	Lys	Met	Ile	Arg	Asn	Pro	Ala	Ser	Leu	Lys	875	880	885
	Ile	Val	Ala	Arg	Glu	Asn	Gly	Gly	Ala	Ser	His	Pro	Leu	Leu	Asp	890	895	900
30	Gln	Arg	Gln	Pro	His	Tyr	Ser	Ala	Phe	Gly	Ser	Val	Gly	Glu	Trp	905	910	915
	Leu	Arg	Ala	Ile	Lys	Met	Gly	Arg	Tyr	Glu	Glu	Ser	Phe	Ala	Ala	920	925	930
35	Ala	Gly	Phe	Gly	Ser	Phe	Glu	Leu	Val	Ser	Gln	Ile	Ser	Ala	Glu	935	940	945
	Asp	Leu	Leu	Arg	Ile	Gly	Val	Thr	Leu	Ala	Gly	His	Gln	Lys	Lys	950	955	960
40	Ile	Leu	Ala	Ser	Val	Gln	His	Met	Lys	Ser	Gln	Ala	Lys	Pro	Gly	965	970	975
	Thr	Pro	Gly	Gly	Thr	Gly	Gly	Pro	Ala	Pro	Gln	Tyr				980	985	
45	<210> 89 <211> 911 <212> PRT <213> Homo Sapien																	
50	<400> 89 Met Ala Gln Leu Phe Leu Pro Leu Leu Ala Ala Leu Val Leu Ala 1 5 10 15																	
55	Gln Ala Pro Ala Ala Leu Ala Asp Val Leu Glu Gly Asp Ser Ser 20 25 30																	

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	Glu Asp Arg Ala Phe Arg Val Arg Ile Ala Gly Asp Ala Pro Leu	35	40	45
5	Gln Gly Val Leu Gly Gly Ala Leu Thr Ile Pro Cys His Val His	50	55	60
	Tyr Leu Arg Pro Pro Pro Ser Arg Arg Ala Val Leu Gly Ser Pro	65	70	75
10	Arg Val Lys Trp Thr Phe Leu Ser Arg Gly Arg Glu Ala Glu Val	80	85	90
	Leu Val Ala Arg Gly Val Arg Val Lys Val Asn Glu Ala Tyr Arg	95	100	105
15	Phe Arg Val Ala Leu Pro Ala Tyr Pro Ala Ser Leu Thr Asp Val	110	115	120
	Ser Leu Ala Leu Ser Glu Leu Arg Pro Asn Asp Ser Gly Ile Tyr	125	130	135
20	Arg Cys Glu Val Gln His Gly Ile Asp Asp Ser Ser Asp Ala Val	140	145	150
	Glu Val Lys Val Lys Gly Val Val Phe Leu Tyr Arg Glu Gly Ser	155	160	165
25	Ala Arg Tyr Ala Phe Ser Phe Ser Gly Ala Gln Glu Ala Cys Ala	170	175	180
	Arg Ile Gly Ala His Ile Ala Thr Pro Glu Gln Leu Tyr Ala Ala	185	190	195
30	Tyr Leu Gly Gly Tyr Glu Gln Cys Asp Ala Gly Trp Leu Ser Asp	200	205	210
	Gln Thr Val Arg Tyr Pro Ile Gln Thr Pro Arg Glu Ala Cys Tyr	215	220	225
35	Gly Asp Met Asp Gly Phe Pro Gly Val Arg Asn Tyr Gly Val Val	230	235	240
	Asp Pro Asp Asp Leu Tyr Asp Val Tyr Cys Tyr Ala Glu Asp Leu	245	250	255
40	Asn Gly Glu Leu Phe Leu Gly Asp Pro Pro Glu Lys Leu Thr Leu	260	265	270
	Glu Glu Ala Arg Ala Tyr Cys Gln Glu Arg Gly Ala Glu Ile Ala	275	280	285
45	Thr Thr Gly Gln Leu Tyr Ala Ala Trp Asp Gly Gly Leu Asp His	290	295	300
	Cys Ser Pro Gly Trp Leu Ala Asp Gly Ser Val Arg Tyr Pro Ile	305	310	315
50	Val Thr Pro Ser Gln Arg Cys Gly Gly Gly Leu Pro Gly Val Lys	320	325	330
55	Thr Leu Phe Leu Phe Pro Asn Gln Thr Gly Phe Pro Asn Lys His			

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					335					340					345
5	Ser	Arg	Phe	Asn	Val	Tyr	Cys	Phe	Arg	Asp	Ser	Ala	Gln	Pro	Ser
					350					355					360
	Ala	Ile	Pro	Glu	Ala	Ser	Asn	Pro	Ala	Ser	Asn	Pro	Ala	Ser	Asp
					365					370					375
10	Gly	Leu	Glu	Ala	Ile	Val	Thr	Val	Thr	Glu	Thr	Leu	Glu	Glu	Leu
					380					385					390
	Gln	Leu	Pro	Gln	Glu	Ala	Thr	Glu	Ser	Glu	Ser	Arg	Gly	Ala	Ile
					395					400					405
15	Tyr	Ser	Ile	Pro	Ile	Met	Glu	Asp	Gly	Gly	Gly	Gly	Ser	Ser	Thr
					410					415					420
	Pro	Glu	Asp	Pro	Ala	Glu	Ala	Pro	Arg	Thr	Leu	Leu	Glu	Phe	Glu
					425					430					435
20	Thr	Gln	Ser	Met	Val	Pro	Pro	Thr	Gly	Phe	Ser	Glu	Glu	Glu	Gly
					440					445					450
	Lys	Ala	Leu	Glu	Glu	Glu	Glu	Lys	Tyr	Glu	Asp	Glu	Glu	Glu	Lys
					455					460					465
25	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Val	Glu	Asp	Glu	Ala	Leu	Trp
					470					475					480
	Ala	Trp	Pro	Ser	Glu	Leu	Ser	Ser	Pro	Gly	Pro	Glu	Ala	Ser	Leu
					485					490					495
30	Pro	Thr	Glu	Pro	Ala	Ala	Gln	Glu	Lys	Ser	Leu	Ser	Gln	Ala	Pro
					500					505					510
	Ala	Arg	Ala	Val	Leu	Gln	Pro	Gly	Ala	Ser	Pro	Leu	Pro	Asp	Gly
					515					520					525
35	Glu	Ser	Glu	Ala	Ser	Arg	Pro	Pro	Arg	Val	His	Gly	Pro	Pro	Thr
					530					535					540
	Glu	Thr	Leu	Pro	Thr	Pro	Arg	Glu	Arg	Asn	Leu	Ala	Ser	Pro	Ser
					545					550					555
40	Pro	Ser	Thr	Leu	Val	Glu	Ala	Arg	Glu	Val	Gly	Glu	Ala	Thr	Gly
					560					565					570
	Gly	Pro	Glu	Leu	Ser	Gly	Val	Pro	Arg	Gly	Glu	Ser	Glu	Glu	Thr
					575					580					585
45	Gly	Ser	Ser	Glu	Gly	Ala	Pro	Ser	Leu	Leu	Pro	Ala	Thr	Arg	Ala
					590					595					600
	Pro	Glu	Gly	Thr	Arg	Glu	Leu	Glu	Ala	Pro	Ser	Glu	Asp	Asn	Ser
					605					610					615
50	Gly	Arg	Thr	Ala	Pro	Ala	Gly	Thr	Ser	Val	Gln	Ala	Gln	Pro	Val
					620					625					630
	Leu	Pro	Thr	Asp	Ser	Ala	Ser	Arg	Gly	Gly	Val	Ala	Val	Val	Pro
55					635					640					645

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5	Ala Ser Gly Asp Cys Val Pro Ser Pro Cys His Asn Gly Gly Thr	650	655	660
	Cys Leu Glu Glu Glu Glu Gly Val Arg Cys Leu Cys Leu Pro Gly	665	670	675
10	Tyr Gly Gly Asp Leu Cys Asp Val Gly Leu Arg Phe Cys Asn Pro	680	685	690
	Gly Trp Asp Ala Phe Gln Gly Ala Cys Tyr Lys His Phe Ser Thr	695	700	705
15	Arg Arg Ser Trp Glu Glu Ala Glu Thr Gln Cys Arg Met Tyr Gly	710	715	720
	Ala His Leu Ala Ser Ile Ser Thr Pro Glu Glu Gln Asp Phe Ile	725	730	735
20	Asn Asn Arg Tyr Arg Glu Tyr Gln Trp Ile Gly Leu Asn Asp Arg	740	745	750
	Thr Ile Glu Gly Asp Phe Leu Trp Ser Asp Gly Val Pro Leu Leu	755	760	765
25	Tyr Glu Asn Trp Asn Pro Gly Gln Pro Asp Ser Tyr Phe Leu Ser	770	775	780
	Gly Glu Asn Cys Val Val Met Val Trp His Asp Gln Gly Gln Trp	785	790	795
30	Ser Asp Val Pro Cys Asn Tyr His Leu Ser Tyr Thr Cys Lys Met	800	805	810
	Gly Leu Val Ser Cys Gly Pro Pro Pro Glu Leu Pro Leu Ala Gln	815	820	825
35	Val Phe Gly Arg Pro Arg Leu Arg Tyr Glu Val Asp Thr Val Leu	830	835	840
	Arg Tyr Arg Cys Arg Glu Gly Leu Ala Gln Arg Asn Leu Pro Leu	845	850	855
40	Ile Arg Cys Gln Glu Asn Gly Arg Trp Glu Ala Pro Gln Ile Ser	860	865	870
	Cys Val Pro Arg Arg Pro Ala Arg Ala Leu His Pro Glu Glu Asp	875	880	885
45	Pro Glu Gly Arg Gln Gly Arg Leu Leu Gly Arg Trp Lys Ala Leu	890	895	900
50	Leu Ile Pro Pro Ser Ser Pro Met Pro Gly Pro	905	910	
	<210> 90			
	<211> 671			
	<212> PRT			
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55	<400> 90			

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	Met	Ala	Gln	Leu	Phe	Leu	Pro	Leu	Leu	Ala	Ala	Leu	Val	Leu	Ala	
	1				5					10					15	
5	Gln	Ala	Pro	Ala	Ala	Leu	Ala	Asp	Val	Leu	Glu	Gly	Asp	Ser	Ser	
					20					25					30	
	Glu	Asp	Arg	Ala	Phe	Arg	Val	Arg	Ile	Ala	Gly	Asp	Ala	Pro	Leu	
					35					40					45	
10	Gln	Gly	Val	Leu	Gly	Gly	Ala	Leu	Thr	Ile	Pro	Cys	His	Val	His	
					50					55					60	
	Tyr	Leu	Arg	Pro	Pro	Pro	Ser	Arg	Arg	Ala	Val	Leu	Gly	Ser	Pro	
					65					70					75	
15	Arg	Val	Lys	Trp	Thr	Phe	Leu	Ser	Arg	Gly	Arg	Glu	Ala	Glu	Val	
					80					85					90	
	Leu	Val	Ala	Arg	Gly	Val	Arg	Val	Lys	Val	Asn	Glu	Ala	Tyr	Arg	
					95					100					105	
20	Phe	Arg	Val	Ala	Leu	Pro	Ala	Tyr	Pro	Ala	Ser	Leu	Thr	Asp	Val	
					110					115					120	
	Ser	Leu	Ala	Leu	Ser	Glu	Leu	Arg	Pro	Asn	Asp	Ser	Gly	Ile	Tyr	
25					125					130					135	
	Arg	Cys	Glu	Val	Gln	His	Gly	Ile	Asp	Asp	Ser	Ser	Asp	Ala	Val	
					140					145					150	
	Glu	Val	Lys	Val	Lys	Gly	Val	Val	Phe	Leu	Tyr	Arg	Glu	Gly	Ser	
30					155					160					165	
	Ala	Arg	Tyr	Ala	Phe	Ser	Phe	Ser	Gly	Ala	Gln	Glu	Ala	Cys	Ala	
					170					175					180	
	Arg	Ile	Gly	Ala	His	Ile	Ala	Thr	Pro	Glu	Gln	Leu	Tyr	Ala	Ala	
35					185					190					195	
	Tyr	Leu	Gly	Gly	Tyr	Glu	Gln	Cys	Asp	Ala	Gly	Trp	Leu	Ser	Asp	
					200					205					210	
	Gln	Thr	Val	Arg	Tyr	Pro	Ile	Gln	Thr	Pro	Arg	Glu	Ala	Cys	Tyr	
40					215					220					225	
	Gly	Asp	Met	Asp	Gly	Phe	Pro	Gly	Val	Arg	Asn	Tyr	Gly	Val	Val	
					230					235					240	
45	Asp	Pro	Asp	Asp	Leu	Tyr	Asp	Val	Tyr	Cys	Tyr	Ala	Glu	Asp	Leu	
					245					250					255	
	Asn	Gly	Glu	Leu	Phe	Leu	Gly	Asp	Pro	Pro	Glu	Lys	Leu	Thr	Leu	
					260					265					270	
50	Glu	Glu	Ala	Arg	Ala	Tyr	Cys	Gln	Glu	Arg	Gly	Ala	Glu	Ile	Ala	
					275					280					285	
	Thr	Thr	Gly	Gln	Leu	Tyr	Ala	Ala	Trp	Asp	Gly	Gly	Leu	Asp	His	
					290					295					300	
55	Cys	Ser	Pro	Gly	Trp	Leu	Ala	Asp	Gly	Ser	Val	Arg	Tyr	Pro	Ile	

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					305					310					315
5	Val	Thr	Pro	Ser	Gln	Arg	Cys	Gly	Gly	Gly	Leu	Pro	Gly	Val	Lys
					320					325					330
	Thr	Leu	Phe	Leu	Phe	Pro	Asn	Gln	Thr	Gly	Phe	Pro	Asn	Lys	His
					335					340					345
10	Ser	Arg	Phe	Asn	Val	Tyr	Cys	Phe	Arg	Asp	Ser	Ala	Gln	Pro	Ser
					350					355					360
	Ala	Ile	Pro	Glu	Ala	Ser	Asn	Pro	Ala	Ser	Asn	Pro	Ala	Ser	Asp
					365					370					375
15	Gly	Leu	Glu	Ala	Ile	Val	Thr	Val	Thr	Glu	Thr	Leu	Glu	Glu	Leu
					380					385					390
	Gln	Leu	Pro	Gln	Glu	Ala	Thr	Glu	Ser	Glu	Ser	Arg	Gly	Ala	Ile
					395					400					405
20	Tyr	Ser	Ile	Pro	Ile	Met	Glu	Asp	Gly	Gly	Gly	Gly	Ser	Ser	Thr
					410					415					420
	Pro	Glu	Asp	Pro	Ala	Glu	Ala	Pro	Arg	Thr	Leu	Leu	Glu	Phe	Glu
					425					430					435
25	Thr	Gln	Ser	Met	Val	Pro	Pro	Thr	Gly	Phe	Ser	Glu	Glu	Glu	Gly
					440					445					450
	Lys	Ala	Leu	Glu	Glu	Glu	Glu	Lys	Tyr	Glu	Asp	Glu	Glu	Glu	Lys
					455					460					465
30	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Val	Glu	Asp	Glu	Ala	Leu	Trp
					470					475					480
	Ala	Trp	Pro	Ser	Glu	Leu	Ser	Ser	Pro	Gly	Pro	Glu	Ala	Ser	Leu
					485					490					495
35	Pro	Thr	Glu	Pro	Ala	Ala	Gln	Glu	Glu	Ser	Leu	Ser	Gln	Ala	Pro
					500					505					510
	Ala	Arg	Ala	Val	Leu	Gln	Pro	Gly	Ala	Ser	Pro	Leu	Pro	Asp	Gly
					515					520					525
40	Glu	Ser	Glu	Ala	Ser	Arg	Pro	Pro	Arg	Val	His	Gly	Pro	Pro	Thr
					530					535					540
	Glu	Thr	Leu	Pro	Thr	Pro	Arg	Glu	Arg	Asn	Leu	Ala	Ser	Pro	Ser
					545					550					555
45	Pro	Ser	Thr	Leu	Val	Glu	Ala	Arg	Glu	Val	Gly	Glu	Ala	Thr	Gly
					560					565					570
	Gly	Pro	Glu	Leu	Ser	Gly	Val	Pro	Arg	Gly	Glu	Ser	Glu	Glu	Thr
					575					580					585
50	Gly	Ser	Ser	Glu	Gly	Ala	Pro	Ser	Leu	Leu	Pro	Ala	Thr	Arg	Ala
					590					595					600
55	Pro	Glu	Gly	Thr	Arg	Glu	Leu	Glu	Ala	Pro	Ser	Glu	Asp	Asn	Ser
					605					610					615

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Gly Arg Thr Ala Pro Ala Gly Thr Ser Val Gln Ala Gln Pro Val
 620 625 630
 5
 Leu Pro Thr Asp Ser Ala Ser Arg Gly Gly Val Ala Val Val Pro
 635 640 645
 Ala Ser Gly Asn Ser Ala Gln Gly Ser Thr Ala Leu Ser Ile Leu
 650 655 660
 10
 Leu Leu Phe Phe Pro Leu Gln Leu Trp Val Thr
 665 670
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 15
 <400> 91
 Met Ala Val Arg Gln Trp Val Ile Ala Leu Ala Leu Ala Ala Leu
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 Leu Val Val Asp Arg Glu Val Pro Val Ala Ala Gly Lys Leu Pro
 20 25 30
 Phe Ser Arg Met Pro Ile Cys Glu His Met Val Glu Ser Pro Thr
 35 40 45
 25
 Cys Ser Gln Met Ser Asn Leu Val Cys Gly Thr Asp Gly Leu Thr
 50 55 60
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 Tyr Thr Asn Glu Cys Gln Leu Cys Leu Ala Arg Ile Lys Thr Lys
 65 70 75
 Gln Asp Ile Gln Ile Met Lys Asp Gly Lys Cys
 80 85
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 Met Ala Pro Leu Cys Pro Ser Pro Trp Leu Pro Leu Leu Ile Pro
 1 5 10 15
 Ala Pro Ala Pro Gly Leu Thr Val Gln Leu Leu Leu Ser Leu Leu
 20 25 30
 45
 Leu Leu Val Pro Val His Pro Gln Arg Leu Pro Arg Met Gln Glu
 35 40 45
 Asp Ser Pro Leu Gly Gly Gly Ser Ser Gly Glu Asp Asp Pro Leu
 50 55 60
 50
 Gly Glu Glu Asp Leu Pro Ser Glu Glu Asp Ser Pro Arg Glu Glu
 65 70 75
 Asp Pro Pro Gly Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro
 80 85 90
 55

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	Gly	Glu	Glu	Asp	Leu	Pro	Glu	Val	Lys	Pro	Lys	Ser	Glu	Glu	Glu	
					95					100					105	
5	Gly	Ser	Leu	Lys	Leu	Glu	Asp	Leu	Pro	Thr	Val	Glu	Ala	Pro	Gly	
					110					115					120	
	Asp	Pro	Gln	Glu	Pro	Gln	Asn	Asn	Ala	His	Arg	Asp	Lys	Glu	Gly	
					125					130					135	
10	Asp	Asp	Gln	Ser	His	Trp	Arg	Tyr	Gly	Gly	Asp	Pro	Pro	Trp	Pro	
					140					145					150	
	Arg	Val	Ser	Pro	Ala	Cys	Ala	Gly	Arg	Phe	Gln	Ser	Pro	Val	Asp	
					155					160					165	
15	Ile	Arg	Pro	Gln	Leu	Ala	Ala	Phe	Cys	Pro	Ala	Leu	Arg	Pro	Leu	
					170					175					180	
	Glu	Leu	Leu	Gly	Phe	Gln	Leu	Pro	Pro	Leu	Pro	Glu	Leu	Arg	Leu	
					185					190					195	
20	Arg	Asn	Asn	Gly	His	Ser	Val	Gln	Leu	Thr	Leu	Pro	Pro	Gly	Leu	
					200					205					210	
	Glu	Met	Ala	Leu	Gly	Pro	Gly	Arg	Glu	Tyr	Arg	Ala	Leu	Gln	Leu	
					215					220					225	
25	His	Leu	His	Trp	Gly	Ala	Ala	Gly	Arg	Pro	Gly	Ser	Glu	His	Thr	
					230					235					240	
	Val	Glu	Gly	His	Arg	Phe	Pro	Ala	Glu	Ile	His	Val	Val	His	Leu	
30					245					250					255	
	Ser	Thr	Ala	Phe	Ala	Arg	Val	Asp	Glu	Ala	Leu	Gly	Arg	Pro	Gly	
					260					265					270	
	Gly	Leu	Ala	Val	Leu	Ala	Ala	Phe	Leu	Glu	Glu	Gly	Pro	Glu	Glu	
35					275					280					285	
	Asn	Ser	Ala	Tyr	Glu	Gln	Leu	Leu	Ser	Arg	Leu	Glu	Glu	Ile	Ala	
					290					295					300	
	Glu	Glu	Gly	Ser	Glu	Thr	Gln	Val	Pro	Gly	Leu	Asp	Ile	Ser	Ala	
40					305					310					315	
	Leu	Leu	Pro	Ser	Asp	Phe	Ser	Arg	Tyr	Phe	Arg	Tyr	Glu	Gly	Ser	
					320					325					330	
45	Leu	Thr	Thr	Pro	Pro	Cys	Ala	Gln	Gly	Val	Ile	Trp	Thr	Val	Phe	
					335					340					345	
	Asn	Gln	Thr	Val	Met	Leu	Ser	Ala	Lys	Gln	Leu	His	Thr	Leu	Ser	
					350					355					360	
50	Asp	Thr	Leu	Trp	Gly	Pro	Gly	Asp	Ser	Arg	Leu	Gln	Leu	Asn	Phe	
					365					370					375	
	Arg	Ala	Thr	Gln	Pro	Leu	Asn	Gly	Arg	Val	Ile	Glu	Ala	Ser	Phe	
					380					385					390	
55	Pro	Ala	Gly	Val	Asp	Ser	Ser	Pro	Arg	Ala	Ala	Glu	Pro	Val	Gln	

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		395		400		405
5	Leu Asn Ser Cys	Leu Ala Ala Gly Asp	Ile Leu Ala Leu Val	Phe		
		410		415		420
	Gly Leu Leu Phe	Ala Val Thr Ser Val	Ala Phe Leu Val Gln	Met		
		425		430		435
10	Arg Arg Gln His	Arg Arg Gly Thr Lys	Gly Gly Val Ser Tyr	Arg		
		440		445		450
	Pro Ala Glu Val	Ala Glu Thr Gly Ala				
		455				
15	<210> 93					
	<211> 375					
	<212> PRT					
	<213> Homo Sapien					
	<400> 93					
20	Met Asp Ala Leu	Gln Leu Ala Asn Ser	Ala Phe Ala Val Asp	Leu		
	1	5	10	15		
	Phe Lys Gln Leu	Cys Glu Lys Glu Pro	Leu Gly Asn Val Leu	Phe		
		20	25	30		
25	Ser Pro Ile Cys	Leu Ser Thr Ser Leu	Ser Leu Ala Gln Val	Gly		
		35	40	45		
	Ala Lys Gly Asp	Thr Ala Asn Glu Ile	Gly Gln Val Leu His	Phe		
		50	55	60		
30	Glu Asn Val Lys	Asp Val Pro Phe Gly	Phe Gln Thr Val Thr	Ser		
		65	70	75		
	Asp Val Asn Lys	Leu Ser Ser Phe Tyr	Ser Leu Lys Leu Ile	Lys		
		80	85	90		
35	Arg Leu Tyr Val	Asp Lys Ser Leu Asn	Leu Ser Thr Glu Phe	Ile		
		95	100	105		
	Ser Ser Thr Lys	Arg Pro Tyr Ala Lys	Glu Leu Glu Thr Val	Asp		
		110	115	120		
40	Phe Lys Asp Lys	Leu Glu Glu Thr Lys	Gly Gln Ile Asn Asn	Ser		
		125	130	135		
	Ile Lys Asp Leu	Thr Asp Gly His Phe	Glu Asn Ile Leu Ala	Asp		
		140	145	150		
45	Asn Ser Val Asn	Asp Gln Thr Lys Ile	Leu Val Val Asn Ala	Ala		
		155	160	165		
	Tyr Phe Val Gly	Lys Trp Met Lys Lys	Phe Ser Glu Ser Glu	Thr		
		170	175	180		
50	Lys Glu Cys Pro	Phe Arg Val Asn Lys	Thr Asp Thr Lys Pro	Val		
		185	190	195		
55	Gln Met Met Asn	Met Glu Ala Thr Phe	Cys Met Gly Asn Ile	Asp		
		200	205	210		

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5	Ser Ile Asn Cys Lys Ile Ile Glu Leu Pro Phe Gln Asn Lys His	215	220	225
	Leu Ser Met Phe Ile Leu Leu Pro Lys Asp Val Glu Asp Glu Ser	230	235	240
10	Thr Gly Leu Glu Lys Ile Glu Lys Gln Leu Asn Ser Glu Ser Leu	245	250	255
	Ser Gln Trp Thr Asn Pro Ser Thr Met Ala Asn Ala Lys Val Lys	260	265	270
15	Leu Ser Ile Pro Lys Phe Lys Val Glu Lys Met Ile Asp Pro Lys	275	280	285
	Ala Cys Leu Glu Asn Leu Gly Leu Lys His Ile Phe Ser Glu Asp	290	295	300
20	Thr Ser Asp Phe Ser Gly Met Ser Glu Thr Lys Gly Val Ala Leu	305	310	315
	Ser Asn Val Ile His Lys Val Cys Leu Glu Ile Thr Glu Asp Gly	320	325	330
25	Gly Asp Ser Ile Glu Val Pro Gly Ala Arg Ile Leu Gln His Lys	335	340	345
	Asp Glu Leu Asn Ala Asp His Pro Phe Ile Tyr Ile Ile Arg His	350	355	360
30	Asn Lys Thr Arg Asn Ile Ile Phe Phe Gly Lys Phe Cys Ser Pro	365	370	375
35	<210> 94 <211> 260 <212> PRT <213> Homo Sapien			
40	<400> 94 Met Asp Arg His Ser Ser Tyr Ile Phe Ile Trp Leu Gln Leu Glu 1 5 10 15			
	Leu Cys Ala Met Ala Val Leu Leu Thr Lys Gly Glu Ile Arg Cys	20	25	30
45	Tyr Cys Asp Ala Ala His Cys Val Ala Thr Gly Tyr Met Cys Lys	35	40	45
	Ser Glu Leu Ser Ala Cys Phe Ser Arg Leu Leu Asp Pro Gln Asn	50	55	60
50	Ser Asn Ser Pro Leu Thr His Gly Cys Leu Asp Ser Leu Ala Ser	65	70	75
	Thr Thr Asp Ile Cys Gln Ala Lys Gln Ala Arg Asn His Ser Gly	80	85	90
55	Thr Thr Ile Pro Thr Leu Glu Cys Cys His Glu Asp Met Cys Asn	95	100	105

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	Tyr Arg Gly Leu	His Asp Val Leu Ser	Pro Pro Arg Gly Glu Ala
		110	115 120
5	Ser Gly Gln Gly	Asn Arg Tyr Gln His	Asp Gly Ser Arg Asn Leu
		125	130 135
	Ile Thr Lys Val	Gln Glu Leu Thr Ser	Ser Lys Glu Leu Trp Phe
		140	145 150
10	Arg Ala Ala Val	Ile Ala Val Pro Ile	Ala Gly Gly Leu Ile Leu
		155	160 165
	Val Leu Leu Ile	Met Leu Ala Leu Arg	Met Leu Arg Ser Glu Asn
		170	175 180
15	Lys Arg Leu Gln	Asp Gln Arg Gln Gln	Met Leu Ser Arg Leu His
		185	190 195
	Tyr Ser Phe His	Gly His His Ser Lys	Lys Gly Gln Val Ala Lys
		200	205 210
20	Leu Asp Leu Glu	Cys Met Val Pro Val	Ser Gly His Glu Asn Cys
		215	220 225
	Cys Leu Thr Cys	Asp Lys Met Arg Gln	Ala Asp Leu Ser Asn Asp
		230	235 240
25	Lys Ile Leu Ser	Leu Val His Trp Gly	Met Tyr Ser Gly His Gly
		245	250 255
	Lys Leu Glu Phe	Val	
30		260	
	<210> 95		
	<211> 1095		
	<212> PRT		
	<213> Homo Sapien		
35	<400> 95		
	Met Arg Asn Arg	Arg Asn Asp Thr Leu	Asp Ser Thr Arg Thr Leu
	1	5	10 15
40	Tyr Ser Ser Ala	Ser Arg Ser Thr Asp	Leu Ser Tyr Ser Glu Ser
		20	25 30
	Asp Leu Val Asn	Phe Ile Gln Ala Asn	Phe Lys Lys Arg Glu Cys
		35	40 45
45	Val Phe Phe Thr	Lys Asp Ser Lys Ala	Thr Glu Asn Val Cys Lys
		50	55 60
	Cys Gly Tyr Ala	Gln Ser Gln His Met	Glu Gly Thr Gln Ile Asn
		65	70 75
50	Gln Ser Glu Lys	Trp Asn Tyr Lys Lys	His Thr Lys Glu Phe Pro
		80	85 90
	Thr Asp Ala Phe	Gly Asp Ile Gln Phe	Glu Thr Leu Gly Lys Lys
		95	100 105
55	Gly Lys Tyr Ile	Arg Leu Ser Cys Asp	Thr Asp Ala Glu Ile Leu

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					110					115					120
5	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp	His	Leu	Lys	Thr	Pro	Asn	Leu
					125					130					135
	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys	Asn	Phe	Ala	Leu	Lys	Pro
					140					145					150
10	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile	Tyr	Ile	Ala	Gln	Ser
					155					160					165
	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His	Tyr	Gly	Leu	Thr
					170					175					180
15	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile	Ser	Arg	Ser
					185					190					195
	Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp	Gly	Met
					200					205					210
20	Val	Ser	Asn	Arg	Asp	Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu	Gly
					215					220					225
	Tyr	Phe	Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro
					230					235					240
25	Leu	Tyr	Ile	Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp
					245					250					255
	Asn	Gly	Cys	His	Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn
					260					265					270
30	Gln	Leu	Glu	Lys	His	Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn
					275					280					285
	Tyr	Gly	Gly	Lys	Ile	Pro	Ile	Val	Cys	Phe	Ala	Gln	Gly	Gly	Gly
					290					295					300
35	Lys	Glu	Thr	Leu	Lys	Ala	Ile	Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile
					305					310					315
	Pro	Cys	Val	Val	Val	Glu	Gly	Ser	Gly	Arg	Ile	Ala	Asp	Val	Ile
					320					325					330
40	Ala	Ser	Leu	Val	Glu	Val	Glu	Asp	Ala	Pro	Thr	Ser	Ser	Ala	Val
					335					340					345
	Lys	Glu	Lys	Leu	Val	Arg	Phe	Leu	Pro	Arg	Thr	Val	Ser	Arg	Leu
					350					355					360
45	Ser	Glu	Glu	Glu	Thr	Glu	Ser	Trp	Ile	Lys	Trp	Leu	Lys	Glu	Ile
					365					370					375
	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val	Ile	Lys	Met	Glu	Glu	Ala
					380					385					390
50	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser	Tyr	Ala	Leu	Tyr	Lys
					395					400					405
55	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn	Trp	Asn	Gly	Gln
					410					415					420

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5	Leu	Lys	Leu	Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Asn	Asp	
					425					430					435	
	Glu	Ile	Phe	Thr	Asn	Asp	Arg	Arg	Trp	Glu	Ser	Ala	Asp	Leu	Gln	
					440					445					450	
10	Glu	Val	Met	Phe	Thr	Ala	Leu	Ile	Lys	Asp	Arg	Pro	Lys	Phe	Val	
					455					460					465	
	Arg	Leu	Phe	Leu	Glu	Asn	Gly	Leu	Asn	Leu	Arg	Lys	Phe	Leu	Thr	
					470					475					480	
15	His	Asp	Val	Leu	Thr	Glu	Leu	Phe	Ser	Asn	His	Phe	Ser	Thr	Leu	
					485					490					495	
	Val	Tyr	Arg	Asn	Leu	Gln	Ile	Ala	Lys	Asn	Ser	Tyr	Asn	Asp	Ala	
					500					505					510	
20	Leu	Leu	Thr	Phe	Val	Trp	Lys	Leu	Val	Ala	Asn	Phe	Arg	Arg	Gly	
					515					520					525	
	Phe	Arg	Lys	Glu	Asp	Arg	Asn	Gly	Arg	Asp	Glu	Met	Asp	Ile	Glu	
					530					535					540	
25	Leu	His	Asp	Val	Ser	Pro	Ile	Thr	Arg	His	Pro	Leu	Gln	Ala	Leu	
					545					550					555	
	Phe	Ile	Trp	Ala	Ile	Leu	Gln	Asn	Lys	Lys	Glu	Leu	Ser	Lys	Val	
					560					565					570	
30	Ile	Trp	Glu	Gln	Thr	Arg	Gly	Cys	Thr	Leu	Ala	Ala	Leu	Gly	Ala	
					575					580					585	
	Ser	Lys	Leu	Leu	Lys	Thr	Leu	Ala	Lys	Val	Lys	Asn	Asp	Ile	Asn	
					590					595					600	
35	Ala	Ala	Gly	Glu	Ser	Glu	Glu	Leu	Ala	Asn	Glu	Tyr	Glu	Thr	Arg	
					605					610					615	
	Ala	Val	Glu	Leu	Phe	Thr	Glu	Cys	Tyr	Ser	Ser	Asp	Glu	Asp	Leu	
					620					625					630	
40	Ala	Glu	Gln	Leu	Leu	Val	Tyr	Ser	Cys	Glu	Ala	Trp	Gly	Gly	Ser	
					635					640					645	
	Asn	Cys	Leu	Glu	Leu	Ala	Val	Glu	Ala	Thr	Asp	Gln	His	Phe	Thr	
					650					655					660	
45	Ala	Gln	Pro	Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly	
					665					670					675	
	Glu	Ile	Ser	Arg	Asp	Thr	Lys	Asn	Trp	Lys	Ile	Ile	Leu	Cys	Leu	
					680					685					690	
50	Phe	Ile	Ile	Pro	Leu	Val	Gly	Cys	Gly	Phe	Val	Ser	Phe	Arg	Lys	
					695					700					705	
	Lys	Pro	Val	Asp	Lys	His	Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala	
55					710					715					720	

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	Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe	725	730	735
5	Tyr Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp	740	745	750
	Phe His Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu	755	760	765
10	Val Phe Val Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn	770	775	780
	Gly Val Asn Tyr Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu	785	790	795
15	Gly Leu Phe Tyr Phe Ile Ala Gly Ile Val Phe Arg Leu His Ser	800	805	810
	Ser Asn Lys Ser Ser Leu Tyr Ser Gly Arg Val Ile Phe Cys Leu	815	820	825
20	Asp Tyr Ile Ile Phe Thr Leu Arg Leu Ile His Ile Phe Thr Val	830	835	840
	Ser Arg Asn Leu Gly Pro Lys Ile Ile Met Leu Gln Arg Met Leu	845	850	855
25	Ile Asp Val Phe Phe Phe Leu Phe Leu Phe Ala Val Trp Met Val	860	865	870
	Ala Phe Gly Val Ala Arg Gln Gly Ile Leu Arg Gln Asn Glu Gln	875	880	885
30	Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr Glu Pro Tyr Leu	890	895	900
	Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly Thr Thr Tyr	905	910	915
35	Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys Pro Leu	920	925	930
	Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu Trp	935	940	945
40	Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile	950	955	960
	Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly	965	970	975
45	Thr Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr	980	985	990
	Phe Leu Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro	995	1000	1005
50	Phe Ile Val Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe	1010	1015	1020
55	Lys Cys Cys Cys Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys			

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		1025		1030		1035
5	Phe Lys Asn Glu Asp	Asn Glu Thr Leu Ala Trp Glu Gly Val Met				
		1040		1045		1050
	Lys Glu Asn Tyr Leu Val Lys Ile Asn Thr Lys Ala Asn Asp Thr					
		1055		1060		1065
10	Ser Glu Glu Met Arg His Arg Phe Arg Gln Leu Asp Thr Lys Leu					
		1070		1075		1080
	Asn Asp Leu Lys Gly Leu Leu Lys Glu Ile Ala Asn Lys Ile Lys					
		1085		1090		1095
15	<210> 96					
	<211> 1095					
	<212> PRT					
	<213> Homo Sapien					
20	<400> 96					
	Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu					
	1	5		10		15
	Tyr Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser					
		20		25		30
25	Asp Leu Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys					
		35		40		45
	Val Phe Phe Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys					
		50		55		60
30	Cys Gly Tyr Ala Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn					
		65		70		75
	Gln Ser Glu Lys Trp Asn Tyr Lys Lys His Thr Lys Glu Phe Pro					
		80		85		90
35	Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly Lys Lys					
		95		100		105
	Gly Lys Tyr Ile Arg Leu Ser Cys Asp Thr Asp Ala Glu Ile Leu					
		110		115		120
40	Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys Thr Pro Asn Leu					
		125		130		135
	Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala Leu Lys Pro					
		140		145		150
45	Arg Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala Gln Ser					
		155		160		165
	Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu Met					
		170		175		180
50	Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Ser					
		185		190		195
55	Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp Gly Met					
		200		205		210

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5	Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu Gly	215	220	225
	Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro	230	235	240
10	Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp	245	250	255
	Asn Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn	260	265	270
15	Gln Leu Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn	275	280	285
	Tyr Gly Gly Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly	290	295	300
20	Lys Glu Thr Leu Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile	305	310	315
	Pro Cys Val Val Val Glu Gly Ser Gly Gln Ile Ala Asp Val Ile	320	325	330
25	Ala Ser Leu Val Glu Val Glu Asp Ala Leu Thr Ser Ser Ala Val	335	340	345
	Lys Glu Lys Leu Val Arg Phe Leu Pro Arg Thr Val Ser Arg Leu	350	355	360
30	Pro Glu Glu Glu Thr Glu Ser Trp Ile Lys Trp Leu Lys Glu Ile	365	370	375
	Leu Glu Cys Ser His Leu Leu Thr Val Ile Lys Met Glu Glu Ala	380	385	390
35	Gly Asp Glu Ile Val Ser Asn Ala Ile Ser Tyr Ala Leu Tyr Lys	395	400	405
	Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn Trp Asn Gly Gln	410	415	420
40	Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu Ala Asn Asp	425	430	435
	Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp Leu Gln	440	445	450
45	Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe Val	455	460	465
	Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr	470	475	480
50	His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu	485	490	495
55	Val Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala	500	505	510

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	Leu	Leu	Thr	Phe	Val	Trp	Lys	Leu	Val	Ala	Asn	Phe	Arg	Arg	Gly
					515					520					525
5	Phe	Arg	Lys	Glu	Asp	Arg	Asn	Gly	Arg	Asp	Glu	Met	Asp	Ile	Glu
					530					535					540
	Leu	His	Asp	Val	Ser	Pro	Ile	Thr	Arg	His	Pro	Leu	Gln	Ala	Leu
					545					550					555
10	Phe	Ile	Trp	Ala	Ile	Leu	Gln	Asn	Lys	Lys	Glu	Leu	Ser	Lys	Val
					560					565					570
	Ile	Trp	Glu	Gln	Thr	Arg	Gly	Cys	Thr	Leu	Ala	Ala	Leu	Gly	Ala
					575					580					585
15	Ser	Lys	Leu	Leu	Lys	Thr	Leu	Ala	Lys	Val	Lys	Asn	Asp	Ile	Asn
					590					595					600
	Ala	Ala	Gly	Glu	Ser	Glu	Glu	Leu	Ala	Asn	Glu	Tyr	Glu	Thr	Arg
					605					610					615
20	Ala	Val	Glu	Leu	Phe	Thr	Glu	Cys	Tyr	Ser	Ser	Asp	Glu	Asp	Leu
					620					625					630
	Ala	Glu	Gln	Leu	Leu	Val	Tyr	Ser	Cys	Glu	Ala	Trp	Gly	Gly	Ser
					635					640					645
25	Asn	Cys	Leu	Glu	Leu	Ala	Val	Glu	Ala	Thr	Asp	Gln	His	Phe	Ile
					650					655					660
	Ala	Gln	Pro	Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly
					665					670					675
30	Glu	Ile	Ser	Arg	Asp	Thr	Lys	Asn	Trp	Lys	Ile	Ile	Leu	Cys	Leu
					680					685					690
	Phe	Ile	Ile	Pro	Leu	Val	Gly	Cys	Gly	Phe	Val	Ser	Phe	Arg	Lys
					695					700					705
35	Lys	Pro	Val	Asp	Lys	His	Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala
					710					715					720
	Phe	Phe	Thr	Ser	Pro	Phe	Val	Val	Phe	Ser	Trp	Asn	Val	Val	Phe
					725					730					735
	Tyr	Ile	Ala	Phe	Leu	Leu	Leu	Phe	Ala	Tyr	Val	Leu	Leu	Met	Asp
					740					745					750
45	Phe	His	Ser	Val	Pro	His	Pro	Pro	Glu	Leu	Val	Leu	Tyr	Ser	Leu
					755					760					765
	Val	Phe	Val	Leu	Phe	Cys	Asp	Glu	Val	Arg	Gln	Trp	Tyr	Val	Asn
					770					775					780
50	Gly	Val	Asn	Tyr	Phe	Thr	Asp	Leu	Trp	Asn	Val	Met	Asp	Thr	Leu
					785					790					795
	Gly	Leu	Phe	Tyr	Phe	Ile	Ala	Gly	Ile	Val	Phe	Arg	Leu	His	Ser
					800					805					810
55	Ser	Asn	Lys	Ser	Ser	Leu	Tyr	Ser	Gly	Arg	Val	Ile	Phe	Cys	Leu

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				815					820					825	
5	Asp	Tyr	Ile	Ile	Phe	Thr	Leu	Arg	Leu	Ile	His	Ile	Phe	Thr	Val
				830						835					840
	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile	Ile	Met	Leu	Gln	Arg	Met	Leu
				845						850					855
10	Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu	Phe	Ala	Val	Trp	Met	Val
				860						865					870
	Ala	Phe	Gly	Val	Ala	Arg	Gln	Gly	Ile	Leu	Arg	Gln	Asn	Glu	Gln
				875						880					885
15	Arg	Trp	Arg	Trp	Ile	Phe	Arg	Ser	Val	Ile	Tyr	Glu	Pro	Tyr	Leu
				890						895					900
	Ala	Met	Phe	Gly	Gln	Val	Pro	Ser	Asp	Val	Asp	Gly	Thr	Thr	Tyr
				905						910					915
20	Asp	Phe	Ala	His	Cys	Thr	Phe	Thr	Gly	Asn	Glu	Ser	Lys	Pro	Leu
				920						925					930
	Cys	Val	Glu	Leu	Asp	Glu	His	Asn	Leu	Pro	Arg	Phe	Pro	Glu	Trp
				935						940					945
25	Ile	Thr	Ile	Pro	Leu	Val	Cys	Ile	Tyr	Met	Leu	Ser	Thr	Asn	Ile
				950						955					960
	Leu	Leu	Val	Asn	Leu	Leu	Val	Ala	Met	Phe	Gly	Tyr	Thr	Val	Gly
				965						970					975
30	Thr	Val	Gln	Glu	Asn	Asn	Asp	Gln	Val	Trp	Lys	Phe	Gln	Arg	Tyr
				980						985					990
	Phe	Leu	Val	Gln	Glu	Tyr	Cys	Ser	Arg	Leu	Asn	Ile	Pro	Phe	Pro
				995						1000					1005
35	Phe	Ile	Val	Phe	Ala	Tyr	Phe	Tyr	Met	Val	Val	Lys	Lys	Cys	Phe
				1010						1015					1020
	Lys	Cys	Cys	Cys	Lys	Glu	Lys	Asn	Met	Glu	Ser	Ser	Val	Cys	Cys
				1025						1030					1035
40	Phe	Lys	Asn	Glu	Asp	Asn	Glu	Thr	Leu	Ala	Trp	Glu	Gly	Val	Met
				1040						1045					1050
	Lys	Glu	Asn	Tyr	Leu	Val	Lys	Ile	Asn	Thr	Lys	Ala	Asn	Asp	Thr
				1055						1060					1065
45	Ser	Glu	Glu	Met	Arg	His	Arg	Phe	Arg	Gln	Leu	Asp	Thr	Lys	Leu
				1070						1075					1080
	Asn	Asp	Leu	Lys	Gly	Leu	Leu	Lys	Glu	Ile	Ala	Asn	Lys	Ile	Lys
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					20						25					30	
	Gly	Ala	Asp	Lys	Lys	Pro	Ser	Arg	Cys	Gly	Ser	Gly	Arg	Glu	Gly		
10					35					40						45	
	Glu	Gly	Val	Ser	Glu	Gly	His	Lys	Ser	Met	Thr	Gly	Leu	Tyr	Glu		
					50					55						60	
	Leu	Val	Trp	Arg	Val	Leu	His	Ala	Leu	Leu	Cys	Leu	His	Arg	Thr		
15					65					70						75	
	Leu	Thr	Ser	Trp	Leu	Arg	Val	Arg	Phe	Gly	Thr	Trp	Asn	Trp	Ile		
					80					85						90	
	Trp	Arg	Arg	Cys	Cys	Arg	Ala	Ala	Ser	Ala	Ala	Val	Leu	Ala	Pro		
20					95					100						105	
	Leu	Gly	Phe	Thr	Leu	Arg	Lys	Pro	Pro	Ala	Val	Gly	Arg	Asn	Arg		
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	Arg	His	His	Arg	His	Pro	Arg	Gly	Gly	Ser	Cys	Leu	Ala	Ala	Ala		
25					125					130						135	
	His	His	Arg	Met	Arg	Trp	Arg	Ala	Asp	Gly	Arg	Ser	Leu	Glu	Lys		
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	Leu	Pro	Val	His	Met	Gly	Leu	Val	Ile	Thr	Glu	Val	Glu	Gln	Glu		
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	Pro	Ser	Phe	Ser	Asp	Ile	Ala	Ser	Leu	Val	Val	Trp	Cys	Met	Ala		
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	Val	Gly	Ile	Ser	Tyr	Ile	Ser	Val	Tyr	Asp	His	Gln	Gly	Ile	Phe		
35					185					190						195	
	Lys	Arg	Asn	Asn	Ser	Arg	Leu	Met	Asp	Glu	Ile	Leu	Lys	Gln	Gln		
					200					205						210	
	Gln	Glu	Leu	Leu	Gly	Leu	Asp	Cys	Ser	Lys	Tyr	Ser	Pro	Glu	Phe		
40					215					220						225	
	Ala	Asn	Ser	Asn	Asp	Lys	Asp	Asp	Gln	Val	Leu	Asn	Cys	His	Leu		
					230					235						240	
	Ala	Val	Lys	Val	Leu	Ser	Pro	Glu	Asp	Gly	Lys	Ala	Asp	Ile	Val		
45					245					250						255	
	Arg	Ala	Ala	Gln	Asp	Phe	Cys	Gln	Leu	Val	Ala	Gln	Lys	Gln	Arg		
					260					265						270	
	Arg	Pro	Thr	Asp	Leu	Asp	Val	Asp	Thr	Leu	Ala	Ser	Leu	Leu	Ser		
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55					290					295						300	

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	Val Asp Ser Thr Leu Gly Phe Leu Pro Trp His Ile Arg Leu Thr	305	310	315
5	Glu Ile Val Ser Leu Pro Ser His Leu Asn Ile Ser Tyr Glu Asp	320	325	330
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10	Gly Lys			
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20	Leu Cys Leu His Arg Thr Leu Thr Ser Trp Leu Arg Val Arg Phe	20	25	30
	Gly Thr Trp Asn Trp Ile Trp Arg Arg Cys Cys Arg Ala Ala Ser	35	40	45
25	Ala Ala Val Leu Ala Pro Leu Gly Phe Thr Leu Arg Lys Pro Pro	50	55	60
	Ala Val Gly Arg Asn Arg Arg His His Arg His Pro Arg Gly Gly	65	70	75
30	Ser Cys Leu Ala Ala Ala His His Arg Met Arg Trp Arg Ala Asp	80	85	90
	Gly Arg Ser Leu Glu Lys Leu Pro Val His Met Gly Leu Val Ile	95	100	105
35	Thr Glu Val Glu Gln Glu Pro Ser Phe Ser Asp Ile Ala Ser Leu	110	115	120
	Val Val Trp Cys Met Ala Val Gly Ile Ser Tyr Ile Ser Val Tyr	125	130	135
40	Asp His Gln Gly Ile Phe Lys Arg Asn Asn Ser Arg Leu Met Asp	140	145	150
	Glu Ile Leu Lys Gln Gln Gln Glu Leu Leu Gly Leu Asp Cys Ser	155	160	165
45	Lys Tyr Ser Pro Glu Phe Ala Asn Ser Asn Asp Lys Asp Asp Gln	170	175	180
	Val Leu Asn Cys His Leu Ala Val Lys Val Leu Ser Pro Glu Asp	185	190	195
50	Gly Lys Ala Asp Ile Val Arg Ala Ala Gln Asp Phe Cys Gln Leu	200	205	210
55	Val Ala Gln Lys Gln Lys Arg Pro Thr Asp Leu Asp Val Asp Thr			

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		215		220		225
5	Leu	Ala	Ser	Leu	Leu	Ser
				Ser	Asn	Gly
				Cys	Pro	Asp
				Pro	Asp	Pro
				Asp	Leu	Pro
				230	235	240
	Val	Leu	Lys	Phe	Gly	Pro
				Val	Asp	Ser
				Thr	Leu	Gly
				245	250	255
10	Trp	His	Ile	Arg	Leu	Thr
				Glu	Ile	Val
				Ser	Leu	Pro
				260	265	270
	Asn	Ile	Ser	Tyr	Glu	Asp
				Phe	Phe	Ser
				Ala	Leu	Arg
				275	280	285
15	Ala	Cys	Glu	Gln	Arg	Leu
				Gly	Lys	
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				His	Arg	Lys
	1			5		10
						15
25	Ala	Gln	Leu	Leu	Val	Asn
				Leu	Leu	Thr
				20	25	Phe
						Gly
						Leu
						Glu
						Val
						30
	Cys	Leu	Ala	Ala	Gly	Ile
				Thr	Tyr	Val
				Pro	Pro	Leu
				40		Leu
						Glu
						45
30	Val	Gly	Val	Glu	Glu	Lys
				Phe	Met	Thr
				Met	Val	Leu
				50	55	Gly
						Ile
						Gly
						60
	Pro	Val	Leu	Gly	Leu	Val
				Cys	Val	Pro
				Leu	Leu	Gly
				65	70	Ser
						Ala
						Ser
						75
35	Asp	His	Trp	Arg	Gly	Arg
				Tyr	Gly	Arg
				Arg	Arg	Arg
				80	85	Pro
						Phe
						Ile
						Trp
						90
	Ala	Leu	Ser	Leu	Gly	Ile
				Leu	Leu	Ser
				Leu	Phe	Leu
				95	100	Ile
						Pro
						Arg
						105
40	Ala	Gly	Trp	Leu	Ala	Gly
				Leu	Leu	Cys
				Pro	Asp	Pro
				110	115	Arg
						Pro
						Leu
						120
	Glu	Leu	Ala	Leu	Leu	Ile
				Leu	Gly	Val
				125	130	Gly
						Leu
						Leu
						Asp
						Phe
						Cys
						135
45	Gly	Gln	Val	Cys	Phe	Thr
				Pro	Leu	Glu
				Ala	Leu	Leu
				140	145	Ser
						Asp
						Leu
						150
	Phe	Arg	Asp	Pro	Asp	His
				Cys	Arg	Gln
				Ala	Tyr	Ser
				155	160	Val
						Tyr
						Ala
						165
50	Phe	Met	Ile	Ser	Leu	Gly
				Gly	Cys	Leu
				Gly	Tyr	Leu
				170	175	Leu
						Pro
						Ala
						180
	Ile	Asp	Trp	Asp	Thr	Ser
				Ala	Leu	Ala
				Pro	Tyr	Leu
				185	190	Gly
						Thr
						Gln
						195

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	Glu	Glu	Cys	Leu	Phe	Gly	Leu	Leu	Thr	Leu	Ile	Phe	Leu	Thr	Cys	
					200					205					210	
5	Val	Ala	Ala	Thr	Leu	Leu	Val	Ala	Glu	Glu	Ala	Ala	Leu	Gly	Pro	
					215					220					225	
	Thr	Glu	Pro	Ala	Glu	Gly	Leu	Ser	Ala	Pro	Ser	Leu	Ser	Pro	His	
10					230					235					240	
	Cys	Cys	Pro	Cys	Arg	Ala	Arg	Leu	Ala	Phe	Arg	Asn	Leu	Gly	Ala	
					245					250					255	
	Leu	Leu	Pro	Arg	Leu	His	Gln	Leu	Cys	Cys	Arg	Met	Pro	Arg	Thr	
15					260					265					270	
	Leu	Arg	Arg	Leu	Phe	Val	Ala	Glu	Leu	Cys	Ser	Trp	Met	Ala	Leu	
					275					280					285	
	Met	Thr	Phe	Thr	Leu	Phe	Tyr	Thr	Asp	Phe	Val	Gly	Glu	Gly	Leu	
20					290					295					300	
	Tyr	Gln	Gly	Val	Pro	Arg	Ala	Glu	Pro	Gly	Thr	Glu	Ala	Arg	Arg	
					305					310					315	
	His	Tyr	Asp	Glu	Gly	Val	Arg	Met	Gly	Ser	Leu	Gly	Leu	Phe	Leu	
25					320					325					330	
	Gln	Cys	Ala	Ile	Ser	Leu	Val	Phe	Ser	Leu	Val	Met	Asp	Arg	Leu	
					335					340					345	
	Val	Gln	Arg	Phe	Gly	Thr	Arg	Ala	Val	Tyr	Leu	Ala	Ser	Val	Ala	
30					350					355					360	
	Ala	Phe	Pro	Val	Ala	Ala	Gly	Ala	Thr	Cys	Leu	Ser	His	Ser	Val	
					365					370					375	
	Ala	Val	Val	Thr	Ala	Ser	Ala	Ala	Leu	Thr	Gly	Phe	Thr	Phe	Ser	
35					380					385					390	
	Ala	Leu	Gln	Ile	Leu	Pro	Tyr	Thr	Leu	Ala	Ser	Leu	Tyr	His	Arg	
					395					400					405	
	Glu	Lys	Gln	Val	Phe	Leu	Pro	Lys	Tyr	Arg	Gly	Asp	Thr	Gly	Gly	
40					410					415					420	
	Ala	Ser	Ser	Glu	Asp	Ser	Leu	Met	Thr	Ser	Phe	Leu	Pro	Gly	Pro	
					425					430					435	
	Lys	Pro	Gly	Ala	Pro	Phe	Pro	Asn	Gly	His	Val	Gly	Ala	Gly	Gly	
45					440					445					450	
	Ser	Gly	Leu	Leu	Pro	Pro	Pro	Pro	Ala	Leu	Cys	Gly	Ala	Ser	Ala	
					455					460					465	
	Cys	Asp	Val	Ser	Val	Arg	Val	Val	Val	Gly	Glu	Pro	Thr	Glu	Ala	
50					470					475					480	
	Arg	Val	Val	Pro	Gly	Arg	Gly	Ile	Cys	Leu	Asp	Leu	Ala	Ile	Leu	
55					485					490					495	

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	Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met	500	505	510
5	Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val	515	520	525
	Ser Ala Ala Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln	530	535	540
10	Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala	545	550	
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	Met Ala Leu Arg Arg Leu Gly Ala Ala Leu Leu Leu Leu Pro Leu	1	5	10
20	Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr	20	25	30
	Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu	35	40	45
25	Val Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln	50	55	60
	Val Cys Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr	65	70	75
30	Lys Phe Ile Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met	80	85	90
	Lys Phe Ser Val Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly	95	100	105
35	Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe	110	115	120
	Asp Ser Ala Thr Lys Thr Phe Pro Asn Trp Met Glu Asn Pro Trp	125	130	135
40	Val Lys Val Asp Thr Ile Ala Ala Asp Glu Ser Phe Ser Gln Val	140	145	150
	Asp Leu Gly Gly Arg Val Met Lys Ile Asn Thr Glu Val Arg Ser	155	160	165
45	Phe Gly Pro Val Ser Arg Ser Gly Phe Tyr Leu Ala Phe Gln Asp	170	175	180
	Tyr Gly Gly Cys Met Ser Leu Ile Ala Val Arg Val Phe Tyr Arg	185	190	195
50	Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile Phe Gln Glu Thr	200	205	210
55	Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala Arg Gly Ser			

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					215					220				225
5	Cys	Ile	Ala	Asn	Ala	Glu	Glu	Val	Asp	Val	Pro	Ile	Lys	Tyr
					230					235				240
	Cys	Asn	Gly	Asp	Gly	Glu	Trp	Leu	Val	Pro	Ile	Gly	Arg	Met
					245					250				255
10	Cys	Lys	Ala	Gly	Phe	Glu	Ala	Val	Glu	Asn	Gly	Thr	Val	Arg
					260					265				270
	Gly	Cys	Pro	Ser	Gly	Thr	Phe	Lys	Ala	Asn	Gln	Gly	Asp	Ala
					275					280				285
15	Cys	Thr	His	Cys	Pro	Ile	Asn	Ser	Arg	Thr	Thr	Ser	Glu	Ala
					290					295				300
	Thr	Asn	Cys	Val	Cys	Arg	Asn	Gly	Tyr	Tyr	Arg	Ala	Asp	Leu
					305					310				315
20	Pro	Leu	Asp	Met	Pro	Cys	Thr	Thr	Ile	Pro	Ser	Ala	Pro	Ala
					320					325				330
	Val	Ile	Ser	Ser	Val	Asn	Glu	Thr	Ser	Leu	Met	Leu	Glu	Thr
					335					340				345
25	Pro	Pro	Arg	Asp	Ser	Gly	Gly	Arg	Glu	Asp	Leu	Val	Tyr	Ile
					350					355				360
	Ile	Cys	Lys	Ser	Cys	Gly	Ser	Gly	Arg	Gly	Ala	Cys	Thr	Cys
					365					370				375
30	Gly	Asp	Asn	Val	Gln	Tyr	Ala	Pro	Arg	Gln	Leu	Gly	Leu	Glu
					380					385				390
	Pro	Arg	Ile	Tyr	Ile	Ser	Asp	Leu	Leu	Ala	His	Thr	Gln	Thr
					395					400				405
35	Phe	Glu	Ile	Gln	Ala	Val	Asn	Gly	Val	Thr	Asp	Gln	Ser	Phe
					410					415				420
	Ser	Pro	Gln	Phe	Ala	Ser	Val	Asn	Ile	Thr	Thr	Asn	Gln	Ala
					425					430				435
40	Pro	Ser	Ala	Val	Ser	Ile	Met	His	Gln	Val	Ser	Arg	Thr	Asp
					440					445				450
	Ser	Ile	Thr	Leu	Ser	Trp	Ser	Gln	Pro	Asp	Gln	Pro	Asn	Val
					455					460				465
45	Ile	Leu	Asp	Tyr	Glu	Leu	Gln	Tyr	Tyr	Glu	Lys	Glu	Leu	Glu
					470					475				480
	Tyr	Asn	Ala	Thr	Ala	Ile	Lys	Ser	Pro	Thr	Asn	Thr	Val	Val
					485					490				495
50	Gln	Gly	Leu	Lys	Ala	Gly	Ala	Ile	Tyr	Val	Phe	Gln	Val	Ala
					500					505				510
55	Arg	Thr	Val	Ala	Gly	Tyr	Gly	Arg	Tyr	Ser	Gly	Lys	Met	Phe
					515					520				525

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	Gln Thr Met Thr	Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys	530	535	540
5	Leu Pro Leu Ile	Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu	545	550	555
	Ile Ala Val Val	Val Ile Ala Ile Val Cys Asn Arg Arg Arg Gly	560	565	570
10	Phe Glu Arg Ala	Asp Ser Glu Tyr Thr Asp Lys Leu Gln His Tyr	575	580	585
	Thr Ser Gly His	Met Thr Pro Gly Met Lys Ile Tyr Ile Asp Pro	590	595	600
15	Phe Thr Tyr Glu	Asp Pro Asn Glu Ala Val Arg Glu Phe Ala Lys	605	610	615
	Glu Ile Asp Ile	Ser Cys Val Lys Ile Glu Gln Val Ile Gly Ala	620	625	630
20	Gly Glu Phe Gly	Glu Val Cys Ser Gly His Leu Lys Leu Pro Gly	635	640	645
	Lys Arg Glu Ile	Phe Val Ala Ile Lys Thr Leu Lys Ser Gly Tyr	650	655	660
25	Thr Glu Lys Gln	Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met	665	670	675
	Gly Gln Phe Asp	His Pro Asn Val Ile His Leu Glu Gly Val Val	680	685	690
30	Thr Lys Ser Thr	Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn	695	700	705
	Gly Ser Leu Asp	Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr	710	715	720
35	Val Ile Gln Leu	Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met	725	730	735
	Lys Tyr Leu Ala	Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala	740	745	750
40	Arg Asn Ile Leu	Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp	755	760	765
45	Phe Gly Leu Ser	Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr	770	775	780
	Tyr Thr Ser Ala	Leu Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala	785	790	795
50	Pro Glu Ala Ile	Gln Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val	800	805	810
	Trp Ser Tyr Gly	Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu	815	820	825
55					

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	Arg	Pro	Tyr	Trp	Asp	Met	Thr	Asn	Gln	Asp	Val	Ile	Asn	Ala	Ile	
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5	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro	Met	Asp	Cys	Pro	Ser	Ala	
					845					850					855	
	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys	Asp	Arg	Asn	His	
					860					865					870	
10	Arg	Pro	Lys	Phe	Gly	Gln	Ile	Val	Asn	Thr	Leu	Asp	Lys	Met	Ile	
					875					880					885	
	Arg	Asn	Pro	Asn	Ser	Leu	Lys	Ala	Met	Ala	Pro	Leu	Ser	Ser	Gly	
					890					895					900	
15	Ile	Asn	Leu	Pro	Leu	Leu	Asp	Arg	Thr	Ile	Pro	Asp	Tyr	Thr	Ser	
					905					910					915	
	Phe	Asn	Thr	Val	Asp	Glu	Trp	Leu	Glu	Ala	Ile	Lys	Met	Gly	Gln	
					920					925					930	
20	Tyr	Lys	Glu	Ser	Phe	Ala	Asn	Ala	Gly	Phe	Thr	Ser	Phe	Asp	Val	
					935					940					945	
	Val	Ser	Gln	Met	Met	Met	Glu	Asp	Ile	Leu	Arg	Val	Gly	Leu	Thr	
					950					955					960	
25	Leu	Ala	Gly	His	Gln	Lys	Lys	Ile	Leu	Asn	Ser	Ile	Gln	Val	Met	
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					20					25					30	
	Ala	Glu	Leu	Gly	Trp	Met	Val	His	Pro	Pro	Ser	Gly	Trp	Glu	Glu	
					35					40					45	
45	Val	Ser	Gly	Tyr	Asp	Glu	Asn	Met	Asn	Thr	Ile	Arg	Thr	Tyr	Gln	
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	Val	Cys	Asn	Val	Phe	Glu	Ser	Ser	Gln	Asn	Asn	Trp	Leu	Arg	Thr	
					65					70					75	
50	Lys	Phe	Ile	Arg	Arg	Arg	Gly	Ala	His	Arg	Ile	His	Val	Glu	Met	
					80					85					90	
	Lys	Phe	Ser	Val	Arg	Asp	Cys	Ser	Ser	Ile	Pro	Ser	Val	Pro	Gly	
					95					100					105	
55	Ser	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Tyr	Glu	Ala	Asp	Phe	

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					110					115					120
5	Asp	Ser	Ala	Thr	Lys	Thr	Phe	Pro	Asn	Trp	Met	Glu	Asn	Pro	Trp
					125					130					135
	Val	Lys	Val	Asp	Thr	Ile	Ala	Ala	Asp	Glu	Ser	Phe	Ser	Gln	Val
					140					145					150
10	Asp	Leu	Gly	Gly	Arg	Val	Met	Lys	Ile	Asn	Thr	Glu	Val	Arg	Ser
					155					160					165
	Phe	Gly	Pro	Val	Ser	Arg	Ser	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp
					170					175					180
15	Tyr	Gly	Gly	Cys	Met	Ser	Leu	Ile	Ala	Val	Arg	Val	Phe	Tyr	Arg
					185					190					195
	Lys	Cys	Pro	Arg	Ile	Ile	Gln	Asn	Gly	Ala	Ile	Phe	Gln	Glu	Thr
					200					205					210
20	Leu	Ser	Gly	Ala	Glu	Ser	Thr	Ser	Leu	Val	Ala	Ala	Arg	Gly	Ser
					215					220					225
	Cys	Ile	Ala	Asn	Ala	Glu	Glu	Val	Asp	Val	Pro	Ile	Lys	Leu	Tyr
					230					235					240
25	Cys	Asn	Gly	Asp	Gly	Glu	Trp	Leu	Val	Pro	Ile	Gly	Arg	Cys	Met
					245					250					255
	Cys	Lys	Ala	Gly	Phe	Glu	Ala	Val	Glu	Asn	Gly	Thr	Val	Cys	Arg
					260					265					270
30	Gly	Cys	Pro	Ser	Gly	Thr	Phe	Lys	Ala	Asn	Gln	Gly	Asp	Glu	Ala
					275					280					285
	Cys	Thr	His	Cys	Pro	Ile	Asn	Ser	Arg	Thr	Thr	Ser	Glu	Gly	Ala
					290					295					300
35	Thr	Asn	Cys	Val	Cys	Arg	Asn	Gly	Tyr	Tyr	Arg	Ala	Asp	Leu	Asp
					305					310					315
	Pro	Leu	Asp	Met	Pro	Cys	Thr	Thr	Ile	Pro	Ser	Ala	Pro	Gln	Ala
					320					325					330
40	Val	Ile	Ser	Ser	Val	Asn	Glu	Thr	Ser	Leu	Met	Leu	Glu	Trp	Thr
					335					340					345
	Pro	Pro	Arg	Asp	Ser	Gly	Gly	Arg	Glu	Asp	Leu	Val	Tyr	Asn	Ile
					350					355					360
45	Ile	Cys	Lys	Ser	Cys	Gly	Ser	Gly	Arg	Gly	Ala	Cys	Thr	Arg	Cys
					365					370					375
	Gly	Asp	Asn	Val	Gln	Tyr	Ala	Pro	Arg	Gln	Leu	Gly	Leu	Thr	Glu
					380					385					390
50	Pro	Arg	Ile	Tyr	Ile	Ser	Asp	Leu	Leu	Ala	His	Thr	Gln	Tyr	Thr
					395					400					405
55	Phe	Glu	Ile	Gln	Ala	Val	Asn	Gly	Val	Thr	Asp	Gln	Ser	Pro	Phe
					410					415					420

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5	Ser Pro Gln Phe	Ala Ser Val Asn Ile Thr Thr Asn Gln Ala Ala	425	430	435
	Pro Ser Ala Val	Ser Ile Met His Gln Val Ser Arg Thr Val Asp	440	445	450
10	Ser Ile Thr Leu	Ser Trp Ser Gln Pro Asp Gln Pro Asn Gly Val	455	460	465
	Ile Leu Asp Tyr	Glu Leu Gln Tyr Tyr Glu Lys Glu Leu Ser Glu	470	475	480
15	Tyr Asn Ala Thr	Ala Ile Lys Ser Pro Thr Asn Thr Val Thr Val	485	490	495
	Gln Gly Leu Lys	Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala	500	505	510
20	Arg Thr Val Ala	Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe	515	520	525
	Gln Thr Met Thr	Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys	530	535	540
25	Leu Pro Leu Ile	Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu	545	550	555
	Ile Ala Val Val	Val Ile Ala Ile Val Cys Asn Arg Arg Gly Phe	560	565	570
30	Glu Arg Ala Asp	Ser Glu Tyr Thr Asp Lys Leu Gln His Tyr Thr	575	580	585
	Ser Gly His Met	Thr Pro Gly Met Lys Ile Tyr Ile Asp Pro Phe	590	595	600
35	Thr Tyr Glu Asp	Pro Asn Glu Ala Val Arg Glu Phe Ala Lys Glu	605	610	615
	Ile Asp Ile Ser	Cys Val Lys Ile Glu Gln Val Ile Gly Ala Gly	620	625	630
40	Glu Phe Gly Glu	Val Cys Ser Gly His Leu Lys Leu Pro Gly Lys	635	640	645
	Arg Glu Ile Phe	Val Ala Ile Lys Thr Leu Lys Ser Gly Tyr Thr	650	655	660
45	Glu Lys Gln Arg	Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly	665	670	675
	Gln Phe Asp His	Pro Asn Val Ile His Leu Glu Gly Val Val Thr	680	685	690
50	Lys Ser Thr Pro	Val Met Ile Ile Thr Glu Phe Met Glu Asn Gly	695	700	705
55	Ser Leu Asp Ser	Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val	710	715	720

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	Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys	725	730	735
5	Tyr Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg	740	745	750
	Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe	755	760	765
10	Gly Leu Ser Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr	770	775	780
	Thr Ser Ala Leu Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro	785	790	795
15	Glu Ala Ile Gln Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val Trp	800	805	810
	Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg	815	820	825
20	Pro Tyr Trp Asp Met Thr Asn Gln Asp Val Ile Asn Ala Ile Glu	830	835	840
	Gln Asp Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ser Ala Leu	845	850	855
25	His Gln Leu Met Leu Asp Cys Trp Gln Lys Asp Arg Asn His Arg	860	865	870
	Pro Lys Phe Gly Gln Ile Val Asn Thr Leu Asp Lys Met Ile Arg	875	880	885
30	Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu Ser Ser Gly Ile	890	895	900
	Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr Thr Ser Phe	905	910	915
35	Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly Gln Tyr	920	925	930
40	Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val Val	935	940	945
	Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu	950	955	960
45	Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg	965	970	975
	Ala Gln Met Asn Gln Ile Gln Ser Val Glu Val	980	985	
50	<210> 102			
	<211> 153			
	<212> PRT			
	<213> Homo Sapien			
55	<400> 102			
	Met Asn Phe Ser Thr Ser Ser Ser Ser Phe Ala Tyr Asp Arg Glu			

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	1	5	10	15
5	Phe Leu Arg Thr	Leu Pro Gly Phe Leu	Ile Val Ala Glu Ile Val	
		20	25	30
	Leu Gly Leu Leu Val	Trp Thr Leu Ile	Ala Gly Thr Glu Tyr Phe	
		35	40	45
10	Arg Val Pro Ala	Phe Gly Trp Val Met	Phe Val Ala Val Phe Tyr	
		50	55	60
	Trp Val Leu Thr	Val Phe Phe Leu Ile	Ile Tyr Ile Thr Met Thr	
		65	70	75
15	Tyr Thr Arg Ile	Pro Gln Val Pro Trp	Thr Thr Val Gly Leu Cys	
		80	85	90
	Phe Asn Gly Ser	Ala Phe Val Leu Tyr	Leu Ser Ala Ala Val Val	
		95	100	105
20	Asp Ala Ser Ser	Val Ser Pro Glu Arg	Asp Ser His Asn Phe Asn	
		110	115	120
	Ser Trp Ala Ala	Ser Ser Phe Phe Ala	Phe Leu Val Asn Ile Cys	
		125	130	135
25	Tyr Ala Gly Asn	Thr Tyr Phe Ser Phe	Ile Ala Trp Arg Ser Arg	
		140	145	150
	Thr Ile Gln			
30	<210> 103			
	<211> 153			
	<212> PRT			
	<213> Homo Sapien			
35	<400> 103			
	Met Asn Phe Ser	Thr Ser Ser Ser Ser	Phe Ala Tyr Asp Arg Glu	
	1	5	10	15
40	Phe Leu Arg Thr	Leu Pro Gly Phe Leu	Ile Val Ala Glu Ile Val	
		20	25	30
	Leu Gly Leu Leu Val	Trp Thr Leu Ile	Ala Gly Thr Glu Tyr Phe	
		35	40	45
45	Arg Val Pro Ala	Phe Gly Trp Val Met	Phe Val Ala Val Phe Tyr	
		50	55	60
	Trp Val Leu Thr	Val Phe Phe Leu Ile	Ile Tyr Ile Thr Met Thr	
		65	70	75
50	Tyr Thr Arg Ile	Pro Gln Val Pro Trp	Thr Thr Val Gly Leu Cys	
		80	85	90
	Phe Asn Gly Ser	Ala Phe Val Leu Tyr	Leu Ser Ala Ala Val Val	
		95	100	105
55	Asp Ala Ser Ser	Val Ser Pro Glu Arg	Asp Ser His Asn Phe Asn	
		110	115	120

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Ser Trp Ala Ala Ser Ser Phe Phe Ala Phe Leu Val Thr Ile Cys
 125 130 135
 5
 Tyr Ala Gly Asn Thr Tyr Phe Ser Phe Ile Ala Trp Arg Ser Arg
 140 145 150
 Thr Ile Gln
 10
 <210> 104
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 15
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 Met Pro Thr Thr Val Asp Asp Val Leu Glu His Gly Gly Glu Phe
 1 5 10 15
 His Phe Phe Gln Lys Gln Met Phe Phe Leu Leu Ala Leu Leu Ser
 20 20 25 30
 Ala Thr Phe Ala Pro Ile Tyr Val Gly Ile Val Phe Leu Gly Phe
 35 40 45
 Thr Pro Asp His Arg Cys Arg Ser Pro Gly Val Ala Glu Leu Ser
 25 50 55 60
 Leu Arg Cys Gly Trp Ser Pro Ala Glu Glu Leu Asn Tyr Thr Val
 65 70 75
 Pro Gly Pro Gly Pro Ala Gly Glu Ala Ser Pro Arg Gln Cys Arg
 30 80 85 90
 Arg Tyr Glu Val Asp Trp Asn Gln Ser Thr Phe Asp Cys Val Asp
 95 100 105
 Pro Leu Ala Ser Leu Asp Thr Asn Arg Ser Arg Leu Pro Leu Gly
 35 110 115 120
 Pro Cys Arg Asp Gly Trp Val Tyr Glu Thr Pro Gly Ser Ser Ile
 125 130 135
 Val Thr Glu Phe Asn Leu Val Cys Ala Asn Ser Trp Met Leu Asp
 40 140 145 150
 Leu Phe Gln Ser Ser Val Asn Val Gly Phe Phe Ile Gly Ser Met
 155 160 165
 Ser Ile Gly Tyr Ile Ala Asp Arg Phe Gly Arg Lys Leu Cys Leu
 45 170 175 180
 Leu Thr Thr Val Leu Ile Asn Ala Ala Ala Gly Val Leu Met Ala
 185 190 195
 Ile Ser Pro Thr Tyr Thr Trp Met Leu Ile Phe Arg Leu Ile Gln
 50 200 205 210
 Gly Leu Val Ser Lys Ala Gly Trp Leu Ile Gly Tyr Ile Leu Ile
 215 220 225
 55

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	Thr Glu Phe Val Gly Arg Arg Tyr Arg Arg Thr Val Gly Ile Phe	230	235	240
5	Tyr Gln Val Ala Tyr Thr Val Gly Leu Leu Val Leu Ala Gly Val	245	250	255
	Ala Tyr Ala Leu Pro His Trp Arg Trp Leu Gln Phe Thr Val Ala	260	265	270
10	Leu Pro Asn Phe Phe Phe Leu Leu Tyr Tyr Trp Cys Ile Pro Glu	275	280	285
	Ser Pro Arg Trp Leu Ile Ser Gln Asn Lys Asn Ala Glu Ala Met	290	295	300
15	Arg Ile Ile Lys His Ile Ala Lys Lys Asn Gly Lys Ser Leu Pro	305	310	315
	Ala Ser Leu Gln Arg Leu Arg Leu Glu Glu Glu Thr Gly Lys Lys	320	325	330
20	Leu Asn Pro Ser Phe Leu Asp Leu Val Arg Thr Pro Gln Ile Arg	335	340	345
	Lys His Thr Met Ile Leu Met Tyr Asn Trp Phe Thr Ser Ser Val	350	355	360
25	Leu Tyr Gln Gly Leu Ile Met His Met Gly Leu Ala Gly Asp Asn	365	370	375
	Ile Tyr Leu Asp Phe Phe Tyr Ser Ala Leu Val Glu Phe Pro Ala	380	385	390
30	Ala Phe Met Ile Ile Leu Thr Ile Asp Arg Ile Gly Arg Arg Tyr	395	400	405
	Pro Trp Ala Ala Ser Asn Met Val Ala Gly Ala Ala Cys Leu Ala	410	415	420
35	Ser Val Phe Ile Pro Gly Asp Leu Gln Trp Leu Lys Ile Ile Ile	425	430	435
	Ser Cys Leu Gly Arg Met Gly Ile Thr Met Ala Tyr Glu Ile Val	440	445	450
40	Cys Leu Val Asn Ala Glu Leu Tyr Pro Thr Phe Ile Arg Asn Leu	455	460	465
	Gly Val His Ile Cys Ser Ser Met Cys Asp Ile Gly Gly Ile Ile	470	475	480
	Thr Pro Phe Leu Val Tyr Arg Leu Thr Asn Ile Trp Leu Glu Leu	485	490	495
50	Pro Leu Met Val Phe Gly Val Leu Gly Leu Val Ala Gly Gly Leu	500	505	510
	Val Leu Leu Leu Pro Glu Thr Lys Gly Lys Ala Leu Pro Glu Thr	515	520	525
55	Ile Glu Glu Ala Glu Asn Met Gln Arg Pro Arg Lys Asn Lys Glu			

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					530						535				540
					Lys Met Ile Tyr Leu Gln Val Gln Lys Leu Asp Ile Pro Leu Asn										
5					545						550				555
					<210> 105										
					<211> 555										
					<212> PRT										
10					<213> Homo Sapien										
					<400> 105										
					Met Pro Thr Thr Val Asp Asp Val Leu Glu His Gly Gly Glu Phe										
					1 5						10				15
15					His Phe Phe Gln Lys Gln Met Phe Phe Leu Leu Ala Leu Leu Ser						25				30
					20										
					Ala Thr Phe Ala Pro Ile Tyr Val Gly Ile Val Phe Leu Gly Phe						40				45
					35										
20					Thr Pro Asp His Arg Cys Arg Ser Pro Gly Val Ala Glu Leu Ser						55				60
					50										
					Leu Arg Cys Gly Trp Ser Pro Ala Glu Glu Leu Asn Tyr Thr Val						70				75
					65										
25					Pro Gly Pro Gly Pro Ala Gly Glu Ala Ser Pro Arg Gln Cys Arg						85				90
					80										
					Arg Tyr Glu Val Asp Trp Asn Gln Ser Thr Phe Asp Cys Val Asp						100				105
					95										
30					Pro Leu Ala Ser Leu Asp Thr Asn Arg Ser Arg Leu Pro Leu Gly						115				120
					110										
					Pro Cys Arg Asp Gly Trp Val Tyr Glu Thr Pro Gly Ser Ser Ile						130				135
					125										
35					Val Thr Glu Phe Asn Leu Val Cys Ala Asn Ser Trp Met Leu Asp						145				150
					140										
					Leu Phe Gln Ser Ser Val Asn Val Gly Phe Phe Ile Gly Ser Met						160				165
					155										
40					Ser Ile Gly Tyr Ile Ala Asp Arg Phe Gly Arg Lys Leu Cys Leu						175				180
					170										
					Leu Thr Thr Val Leu Ile Asn Ala Ala Ala Gly Val Leu Met Ala						190				195
					185										
45					Ile Ser Pro Thr Tyr Thr Trp Met Leu Ile Phe Arg Leu Ile Gln						205				210
					200										
					Gly Leu Val Ser Lys Ala Gly Trp Leu Ile Gly Tyr Ile Leu Ile						220				225
50					215										
					Thr Glu Phe Val Gly Arg Arg Tyr Arg Arg Thr Val Gly Ile Phe						235				240
					230										
55					Tyr Gln Val Ala Tyr Thr Val Gly Leu Leu Val Leu Ala Gly Val						250				255
					245										

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	Ala Tyr Ala Leu	Pro His Trp Arg Trp	Leu Gln Phe Thr Val	Ser
		260	265	270
5	Leu Pro Asn Phe	Phe Phe Leu Leu Tyr	Tyr Trp Cys Ile Pro	Glu
		275	280	285
	Ser Pro Arg Trp	Leu Ile Ser Gln Asn	Lys Asn Ala Glu Ala	Met
10		290	295	300
	Arg Ile Ile Lys	His Ile Ala Lys Lys	Asn Gly Lys Ser Leu	Pro
		305	310	315
	Ala Ser Leu Gln	Arg Leu Arg Leu Glu	Glu Glu Thr Gly Lys	Lys
15		320	325	330
	Leu Asn Pro Ser	Phe Leu Asp Leu Val	Arg Thr Pro Gln Ile	Arg
		335	340	345
	Lys His Thr Met	Ile Leu Met Tyr Asn	Trp Phe Thr Ser Ser	Val
20		350	355	360
	Leu Tyr Gln Gly	Leu Ile Met His Met	Gly Leu Ala Gly Asp	Asn
		365	370	375
	Ile Tyr Leu Asp	Phe Phe Tyr Ser Ala	Leu Val Glu Phe Pro	Ala
25		380	385	390
	Ala Phe Met Ile	Ile Leu Thr Ile Asp	Arg Ile Gly Arg Arg	Tyr
		395	400	405
	Pro Trp Ala Ala	Ser Asn Met Val Ala	Gly Ala Ala Cys Leu	Ala
30		410	415	420
	Ser Val Phe Ile	Pro Gly Asp Leu Gln	Trp Leu Lys Ile Ile	Ile
		425	430	435
	Ser Cys Leu Gly	Arg Met Gly Ile Thr	Met Ala Tyr Glu Ile	Val
35		440	445	450
	Cys Leu Val Asn	Ala Glu Leu Tyr Pro	Thr Phe Ile Arg Asn	Leu
		455	460	465
	Gly Val His Ile	Cys Ser Ser Met Cys	Asp Ile Gly Gly Ile	Ile
40		470	475	480
	Thr Pro Phe Leu	Val Tyr Arg Leu Thr	Asn Ile Trp Leu Glu	Leu
		485	490	495
	Pro Leu Met Val	Phe Gly Val Leu Gly	Leu Val Ala Gly Gly	Leu
45		500	505	510
	Val Leu Leu Leu	Pro Glu Thr Lys Gly	Lys Ala Leu Pro Glu	Thr
		515	520	525
	Ile Glu Glu Ala	Glu Asn Met Gln Arg	Pro Arg Lys Asn Lys	Glu
50		530	535	540
	Lys Met Ile Tyr	Leu Gln Val Gln Lys	Leu Asp Ile Pro Leu	Asn
55		545	550	555

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<210> 106
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<212> PRT
5  <213> Homo Sapien

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  Met Ala Pro Trp  Pro Glu Leu Gly Asp Ala Gln Pro Asn Pro Asp
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10  Lys Tyr Leu Glu Gly Ala Ala Gly Gln Gln Pro Thr Ala Pro Asp
              20              25              30
    Lys Ser Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val
              35              40              45
15  Thr Lys Ile Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile
              50              55              60
    Asp Glu Pro Thr Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu
              65              70              75
20  Gln Asp Ser Gly Ile Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys
              80              85              90
    Ile Leu Cys Phe Phe Gln Gly Ile Gly Arg Leu Ile Leu Leu Leu
              95              100             105
25  Gly Phe Leu Tyr Phe Phe Val Cys Ser Leu Asp Ile Leu Ser Ser
              110             115             120
    Ala Phe Gln Leu Val Gly Gly Lys Met Ala Gly Gln Phe Phe Ser
              125             130             135
30  Asn Ser Ser Ile Met Ser Asn Pro Leu Leu Gly Leu Val Ile Gly
              140             145             150
    Val Leu Val Thr Val Leu Val Gln Ser Ser Ser Thr Ser Thr Ser
              155             160             165
35  Ile Val Val Ser Met Val Ser Ser Ser Leu Leu Thr Val Arg Ala
              170             175             180
    Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser Ile Thr
              185             190             195
40  Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser Glu Phe
              200             205             210
    Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp
              215             220             225
45  Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr
              230             235             240
50  Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys
              245             250             255
    Asn Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro
              260             265             270
55  Phe Thr Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln

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					275					280					285
5	Ile	Ala	Met	Asn	Asp 290	Glu	Lys	Ala	Lys	Asn 295	Lys	Ser	Leu	Val	Lys 300
	Ile	Trp	Cys	Lys	Thr 305	Phe	Thr	Asn	Lys	Thr 310	Gln	Ile	Asn	Val	Thr 315
10	Val	Pro	Ser	Thr	Ala 320	Asn	Cys	Thr	Ser	Pro 325	Ser	Leu	Cys	Trp	Thr 330
	Asp	Gly	Ile	Gln	Asn 335	Trp	Thr	Met	Lys	Asn 340	Val	Thr	Tyr	Lys	Glu 345
15	Asn	Ile	Ala	Lys	Cys 350	Gln	His	Ile	Phe	Val 355	Asn	Phe	His	Leu	Pro 360
	Asp	Leu	Ala	Val	Gly 365	Thr	Ile	Leu	Leu	Ile 370	Leu	Ser	Leu	Leu	Val 375
20	Leu	Cys	Gly	Cys	Leu 380	Ile	Met	Ile	Val	Lys 385	Ile	Leu	Gly	Ser	Val 390
	Leu	Lys	Gly	Gln	Val 395	Ala	Thr	Val	Ile	Lys 400	Lys	Thr	Ile	Asn	Thr 405
25	Asp	Phe	Pro	Phe	Pro 410	Phe	Ala	Trp	Leu	Thr 415	Gly	Tyr	Leu	Ala	Ile 420
	Leu	Val	Gly	Ala	Gly 425	Met	Thr	Phe	Ile	Val 430	Gln	Ser	Ser	Ser	Val 435
30	Phe	Thr	Ser	Ala	Leu 440	Thr	Pro	Leu	Ile	Gly 445	Ile	Gly	Val	Ile	Thr 450
	Ile	Glu	Arg	Ala	Tyr 455	Pro	Leu	Thr	Leu	Gly 460	Ser	Asn	Ile	Gly	Thr 465
35	Thr	Thr	Thr	Ala	Ile 470	Leu	Ala	Ala	Leu	Ala 475	Ser	Pro	Gly	Asn	Ala 480
	Leu	Arg	Ser	Ser	Leu 485	Gln	Ile	Ala	Leu	Cys 490	His	Phe	Phe	Phe	Asn 495
40	Ile	Ser	Gly	Ile	Leu 500	Leu	Trp	Tyr	Pro	Ile 505	Pro	Phe	Thr	Arg	Leu 510
	Pro	Ile	Arg	Met	Ala 515	Lys	Gly	Leu	Gly	Asn 520	Ile	Ser	Ala	Lys	Tyr 525
45	Arg	Trp	Phe	Ala	Val 530	Phe	Tyr	Leu	Ile	Ile 535	Phe	Phe	Phe	Leu	Ile 540
	Pro	Leu	Thr	Val	Phe 545	Gly	Leu	Ser	Leu	Ala 550	Gly	Trp	Arg	Val	Leu 555
50	Val	Gly	Val	Gly	Val 560	Pro	Val	Val	Phe	Ile 565	Ile	Ile	Leu	Val	Leu 570
	Cys	Leu	Arg	Leu	Leu 575	Gln	Ser	Arg	Cys	Pro 580	Arg	Val	Leu	Pro	Lys 585
55															

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5	Lys	Leu	Gln	Asn	Trp	Asn	Phe	Leu	Pro	Leu	Trp	Met	Arg	Ser	Leu	590	595	600	
	Lys	Pro	Trp	Asp	Ala	Val	Val	Ser	Lys	Phe	Thr	Gly	Cys	Phe	Gln	605	610	615	
10	Met	Arg	Cys	Cys	Tyr	Cys	Cys	Arg	Val	Cys	Cys	Arg	Ala	Cys	Cys	620	625	630	
	Leu	Leu	Cys	Gly	Cys	Pro	Lys	Cys	Cys	Arg	Cys	Ser	Lys	Cys	Cys	635	640	645	
15	Glu	Asp	Leu	Glu	Glu	Ala	Gln	Glu	Gly	Gln	Asp	Val	Pro	Val	Lys	650	655	660	
	Ala	Pro	Glu	Thr	Phe	Asp	Asn	Ile	Thr	Ile	Ser	Arg	Glu	Ala	Gln	665	670	675	
20	Gly	Glu	Val	Pro	Ala	Ser	Asp	Ser	Lys	Thr	Glu	Cys	Thr	Ala	Leu	680	685	690	
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	<211> 690																		
	<212> PRT																		
25	<213> Homo Sapien																		
	<400> 107																		
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30	Lys	Tyr	Leu	Glu	Gly	Ala	Ala	Gly	Gln	Gln	Pro	Thr	Ala	Pro	Asp	20	25	30	
	Lys	Ser	Lys	Glu	Thr	Asn	Lys	Thr	Asp	Asn	Thr	Glu	Ala	Pro	Val	35	40	45	
35	Thr	Lys	Ile	Glu	Leu	Leu	Pro	Ser	Tyr	Ser	Thr	Ala	Thr	Leu	Ile	50	55	60	
	Asp	Glu	Pro	Thr	Glu	Val	Asp	Asp	Pro	Trp	Asn	Leu	Pro	Thr	Leu	65	70	75	
40	Gln	Asp	Ser	Gly	Ile	Lys	Trp	Ser	Glu	Arg	Asp	Thr	Lys	Gly	Lys	80	85	90	
	Ile	Leu	Cys	Phe	Phe	Gln	Gly	Ile	Gly	Arg	Leu	Ile	Leu	Leu	Leu	95	100	105	
45	Gly	Phe	Leu	Tyr	Phe	Phe	Val	Cys	Ser	Leu	Asp	Ile	Leu	Ser	Ser	110	115	120	
	Ala	Phe	Gln	Leu	Val	Gly	Gly	Lys	Met	Ala	Gly	Gln	Phe	Phe	Ser	125	130	135	
50	Asn	Ser	Ser	Ile	Met	Ser	Asn	Pro	Leu	Leu	Gly	Leu	Val	Ile	Gly	140	145	150	
	Val	Leu	Val	Thr	Val	Leu	Val	Gln	Ser	Ser	Ser	Thr	Ser	Thr	Ser	155	160	165	
55																			

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	Ile Val Val Ser Met Val Ser Ser Ser Leu Leu Thr Val Arg Ala	
	170	175 180
5	Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser Ile Thr	
	185	190 195
	Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser Glu Phe	
	200	205 210
10	Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp	
	215	220 225
	Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr	
	230	235 240
15	Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys	
	245	250 255
	Asn Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro	
	260	265 270
20	Phe Thr Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln	
	275	280 285
	Ile Ala Met Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys	
	290	295 300
25	Ile Trp Cys Lys Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr	
	305	310 315
	Val Pro Ser Thr Ala Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr	
	320	325 330
30	Asp Gly Ile Gln Asn Trp Thr Met Lys Asn Val Thr Tyr Lys Glu	
	335	340 345
	Asn Ile Ala Lys Cys Gln His Ile Phe Val Asn Phe His Leu Pro	
	350	355 360
35	Asp Leu Ala Val Gly Thr Ile Leu Leu Ile Leu Ser Leu Leu Val	
	365	370 375
	Leu Cys Gly Cys Leu Ile Met Ile Val Lys Ile Leu Gly Ser Val	
	380	385 390
40	Leu Lys Gly Gln Val Ala Thr Val Ile Lys Lys Thr Ile Asn Thr	
	395	400 405
	Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly Tyr Leu Ala Ile	
	410	415 420
45	Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser Ser Ser Val	
	425	430 435
50	Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly Val Ile Thr	
	440	445 450
	Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile Gly Thr	
	455	460 465
55	Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn Ala	

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				470					475					480	
5	Leu	Arg	Ser	Ser	Leu	Gln	Ile	Ala	Leu	Cys	His	Phe	Phe	Phe	Asn
					485					490					495
	Ile	Ser	Gly	Ile	Leu	Leu	Trp	Tyr	Pro	Ile	Pro	Phe	Thr	Arg	Leu
					500					505					510
10	Pro	Ile	Arg	Met	Ala	Lys	Gly	Leu	Gly	Asn	Ile	Ser	Ala	Lys	Tyr
					515					520					525
	Arg	Trp	Phe	Ala	Val	Phe	Tyr	Leu	Ile	Ile	Phe	Phe	Phe	Leu	Ile
					530					535					540
15	Pro	Leu	Thr	Val	Phe	Gly	Leu	Ser	Leu	Ala	Gly	Trp	Arg	Val	Leu
					545					550					555
	Val	Gly	Val	Gly	Val	Pro	Val	Val	Phe	Ile	Ile	Ile	Leu	Val	Leu
					560					565					570
20	Cys	Leu	Arg	Leu	Leu	Gln	Ser	Arg	Cys	Pro	Arg	Val	Leu	Pro	Lys
					575					580					585
	Lys	Leu	Gln	Asn	Trp	Asn	Phe	Leu	Pro	Leu	Trp	Met	Arg	Ser	Leu
					590					595					600
25	Lys	Pro	Trp	Asp	Ala	Val	Val	Ser	Lys	Phe	Thr	Gly	Cys	Phe	Gln
					605					610					615
	Met	Arg	Cys	Cys	Cys	Cys	Cys	Arg	Val	Cys	Cys	Arg	Ala	Cys	Cys
					620					625					630
30	Leu	Leu	Cys	Gly	Cys	Pro	Lys	Cys	Cys	Arg	Cys	Ser	Lys	Cys	Cys
					635					640					645
	Glu	Asp	Leu	Glu	Glu	Ala	Gln	Glu	Gly	Gln	Asp	Val	Pro	Val	Lys
					650					655					660
35	Ala	Pro	Glu	Thr	Phe	Asp	Asn	Ile	Thr	Ile	Ser	Arg	Glu	Ala	Gln
					665					670					675
	Gly	Glu	Val	Pro	Ala	Ser	Asp	Ser	Lys	Thr	Glu	Cys	Thr	Ala	Leu
40					680					685					690
	<210> 108														
	<211> 411														
	<212> PRT														
	<213> Homo Sapien														
45	<400> 108														
	Met	Trp	Ser	Gly	Trp	Trp	Leu	Trp	Pro	Leu	Val	Ala	Val	Cys	Thr
	1				5					10				15	
50	Ala	Asp	Phe	Phe	Arg	Asp	Glu	Ala	Glu	Arg	Ile	Met	Arg	Asp	Ser
					20					25				30	
	Pro	Val	Ile	Asp	Gly	His	Asn	Asp	Leu	Pro	Trp	Gln	Leu	Leu	Asp
					35					40				45	
55	Met	Phe	Asn	Asn	Arg	Leu	Gln	Asp	Glu	Arg	Ala	Asn	Leu	Thr	Thr
					50					55				60	

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5	Leu	Ala	Gly	Thr	His	Thr	Asn	Ile	Pro	Lys	Leu	Arg	Ala	Gly	Phe	65	70	75
	Val	Gly	Gly	Gln	Phe	Trp	Ser	Val	Tyr	Thr	Pro	Cys	Asp	Thr	Gln	80	85	90
10	Asn	Lys	Asp	Ala	Val	Arg	Arg	Thr	Leu	Glu	Gln	Met	Asp	Val	Val	95	100	105
	His	Arg	Met	Cys	Arg	Met	Tyr	Pro	Glu	Thr	Phe	Leu	Tyr	Val	Thr	110	115	120
15	Ser	Ser	Ala	Gly	Ile	Arg	Gln	Ala	Phe	Arg	Glu	Gly	Lys	Val	Ala	125	130	135
	Ser	Leu	Ile	Gly	Val	Glu	Gly	Gly	His	Ser	Ile	Asp	Ser	Ser	Leu	140	145	150
20	Gly	Val	Leu	Arg	Ala	Leu	Tyr	Gln	Leu	Gly	Met	Arg	Tyr	Leu	Thr	155	160	165
	Leu	Thr	His	Ser	Cys	Asn	Thr	Pro	Trp	Ala	Asp	Asn	Trp	Leu	Val	170	175	180
25	Asp	Thr	Gly	Asp	Ser	Glu	Pro	Gln	Ser	Gln	Gly	Leu	Ser	Pro	Phe	185	190	195
	Gly	Gln	Arg	Val	Val	Lys	Glu	Leu	Asn	Arg	Leu	Gly	Val	Leu	Ile	200	205	210
30	Asp	Leu	Ala	His	Val	Ser	Val	Ala	Thr	Met	Lys	Ala	Thr	Leu	Gln	215	220	225
	Leu	Ser	Arg	Ala	Pro	Val	Ile	Phe	Ser	His	Ser	Ser	Ala	Tyr	Ser	230	235	240
35	Val	Cys	Ala	Ser	Arg	Arg	Asn	Val	Pro	Asp	Asp	Val	Leu	Arg	Leu	245	250	255
	Val	Lys	Gln	Thr	Asp	Ser	Leu	Val	Met	Val	Asn	Phe	Tyr	Asn	Asn	260	265	270
40	Tyr	Ile	Ser	Cys	Thr	Asn	Lys	Ala	Asn	Leu	Ser	Gln	Val	Ala	Asp	275	280	285
	His	Leu	Asp	His	Ile	Lys	Glu	Val	Ala	Gly	Ala	Arg	Ala	Val	Gly	290	295	300
45	Phe	Gly	Gly	Asp	Phe	Asp	Gly	Val	Pro	Arg	Val	Pro	Glu	Gly	Leu	305	310	315
	Glu	Asp	Val	Ser	Lys	Tyr	Pro	Asp	Leu	Ile	Ala	Glu	Leu	Leu	Arg	320	325	330
50	Arg	Asn	Trp	Thr	Glu	Ala	Glu	Val	Lys	Gly	Ala	Leu	Ala	Asp	Asn	335	340	345
55	Leu	Leu	Arg	Val	Phe	Gln	Ala	Val	Glu	Gln	Ala	Ser	Asn	Leu	Thr	350	355	360

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	Gln	Ala	Pro	Glu	Glu	Glu	Pro	Ile	Pro	Leu	Asp	Gln	Leu	Gly	Gly	
				365						370					375	
5	Ser	Cys	Arg	Thr	His	Tyr	Gly	Tyr	Ser	Ser	Gly	Ala	Ser	Ser	Leu	
					380					385					390	
	His	Arg	His	Trp	Gly	Leu	Leu	Leu	Ala	Ser	Leu	Ala	Pro	Leu	Val	
					395					400					405	
10	Leu	Cys	Leu	Ser	Leu	Leu										
					410											
	<210> 109															
	<211> 320															
15	<212> PRT															
	<213> Homo Sapien															
	<400> 109															
	Met	Ser	Ser	Cys	Asn	Phe	Thr	His	Ala	Thr	Phe	Val	Leu	Ile	Gly	
20	1				5					10					15	
	Ile	Pro	Gly	Leu	Glu	Lys	Ala	His	Phe	Trp	Val	Gly	Phe	Pro	Leu	
					20					25					30	
	Leu	Ser	Met	Tyr	Val	Val	Ala	Met	Phe	Gly	Asn	Cys	Ile	Val	Val	
25					35					40					45	
	Phe	Ile	Val	Arg	Thr	Glu	Arg	Ser	Leu	His	Ala	Pro	Met	Tyr	Leu	
					50					55					60	
	Phe	Leu	Cys	Met	Leu	Ala	Ala	Ile	Asp	Leu	Ala	Leu	Ser	Thr	Ser	
30					65					70					75	
	Thr	Met	Pro	Lys	Ile	Leu	Ala	Leu	Phe	Trp	Phe	Asp	Ser	Arg	Glu	
					80					85					90	
35	Ile	Ser	Phe	Glu	Ala	Cys	Leu	Thr	Gln	Met	Phe	Phe	Ile	His	Ala	
					95					100					105	
	Leu	Ser	Ala	Ile	Glu	Ser	Thr	Ile	Leu	Leu	Ala	Met	Ala	Phe	Asp	
					110					115					120	
40	Arg	Tyr	Val	Ala	Ile	Cys	His	Pro	Leu	Arg	His	Ala	Ala	Val	Leu	
					125					130					135	
	Asn	Asn	Thr	Val	Thr	Ala	Gln	Ile	Gly	Ile	Val	Ala	Val	Val	Arg	
					140					145					150	
45	Gly	Ser	Leu	Phe	Phe	Phe	Pro	Leu	Pro	Leu	Leu	Ile	Lys	Arg	Leu	
					155					160					165	
	Ala	Phe	Cys	His	Ser	Asn	Val	Leu	Ser	His	Ser	Tyr	Cys	Val	His	
					170					175					180	
50	Gln	Asp	Val	Met	Lys	Leu	Ala	Tyr	Ala	Asp	Thr	Leu	Pro	Asn	Val	
					185					190					195	
	Val	Tyr	Gly	Leu	Thr	Ala	Ile	Leu	Leu	Val	Met	Gly	Val	Asp	Val	
					200					205					210	
55	Met	Phe	Ile	Ser	Leu	Ser	Tyr	Phe	Leu	Ile	Ile	Arg	Thr	Val	Leu	

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		215		220		225
5	Gln Leu Pro Ser	Lys Ser Glu Arg Ala	Lys Ala Phe Gly Thr Cys			
		230	235			240
	Val Ser His Ile	Gly Val Val Leu Ala	Phe Tyr Val Pro Leu Ile			
		245	250			255
10	Gly Leu Ser Val	Val His Arg Phe Gly	Asn Ser Leu His Pro Ile			
		260	265			270
	Val Arg Val Val	Met Gly Asp Ile Tyr	Leu Leu Leu Pro Pro Val			
		275	280			285
15	Ile Asn Pro Ile	Ile Tyr Gly Ala Lys	Thr Lys Gln Ile Arg Thr			
		290	295			300
	Arg Val Leu Ala	Met Phe Lys Ile Ser	Cys Asp Lys Asp Leu Gln			
		305	310			315
20	Ala Val Gly Gly	Lys				
		320				
	<210>	110				
	<211>	2314				
25	<212>	PRT				
	<213>	Homo Sapien				
	<400>	110				
	Met Arg Ile Leu Lys	Arg Phe Leu Ala Cys	Ile Gln Leu Leu Cys			
	1	5	10			15
30	Val Cys Arg Leu Asp	Trp Ala Asn Gly Tyr	Tyr Arg Gln Gln Arg			
		20	25			30
	Lys Leu Val Glu Glu	Ile Gly Trp Ser Tyr	Thr Gly Ala Leu Asn			
		35	40			45
35	Gln Lys Asn Trp Gly	Lys Lys Tyr Pro Thr	Cys Asn Ser Pro Lys			
		50	55			60
	Gln Ser Pro Ile Asn	Ile Asp Glu Asp Leu	Thr Gln Val Asn Val			
		65	70			75
40	Asn Leu Lys Lys Leu	Lys Phe Gln Gly Trp	Asp Lys Thr Ser Leu			
		80	85			90
	Glu Asn Thr Phe Ile	His Asn Thr Gly Lys	Thr Val Glu Ile Asn			
		95	100			105
45	Leu Thr Asn Asp Tyr	Arg Val Ser Gly Gly	Val Ser Glu Met Val			
		110	115			120
	Phe Lys Ala Ser Lys	Ile Thr Phe His Trp	Gly Lys Cys Asn Met			
		125	130			135
50	Ser Ser Asp Gly Ser	Glu His Ser Leu Glu	Gly Gln Lys Phe Pro			
		140	145			150
55	Leu Glu Met Gln Ile	Tyr Cys Phe Asp Ala	Asp Arg Phe Ser Ser			
		155	160			165

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5	Phe Glu Glu Ala Val Lys Gly Lys Gly Lys Leu Arg Ala Leu Ser	170	175	180
	Ile Leu Phe Glu Val Gly Thr Glu Glu Asn Leu Asp Phe Lys Ala	185	190	195
10	Ile Ile Asp Gly Val Glu Ser Val Ser Arg Phe Gly Lys Gln Ala	200	205	210
	Ala Leu Asp Pro Phe Ile Leu Leu Asn Leu Leu Pro Asn Ser Thr	215	220	225
15	Asp Lys Tyr Tyr Ile Tyr Asn Gly Ser Leu Thr Ser Pro Pro Cys	230	235	240
	Thr Asp Thr Val Asp Trp Ile Val Phe Lys Asp Thr Val Ser Ile	245	250	255
20	Ser Glu Ser Gln Leu Ala Val Phe Cys Glu Val Leu Thr Met Gln	260	265	270
	Gln Ser Gly Tyr Val Met Leu Met Asp Tyr Leu Gln Asn Asn Phe	275	280	285
25	Arg Glu Gln Gln Tyr Lys Phe Ser Arg Gln Val Phe Ser Ser Tyr	290	295	300
	Thr Gly Lys Glu Glu Ile His Glu Ala Val Cys Ser Ser Glu Pro	305	310	315
30	Glu Asn Val Gln Ala Asp Pro Glu Asn Tyr Thr Ser Leu Leu Val	320	325	330
	Thr Trp Glu Arg Pro Arg Val Val Tyr Asp Thr Met Ile Glu Lys	335	340	345
35	Phe Ala Val Leu Tyr Gln Gln Leu Asp Gly Glu Asp Gln Thr Lys	350	355	360
	His Glu Phe Leu Thr Asp Gly Tyr Gln Asp Leu Gly Ala Ile Leu	365	370	375
40	Asn Asn Leu Leu Pro Asn Met Ser Tyr Val Leu Gln Ile Val Ala	380	385	390
	Ile Cys Thr Asn Gly Leu Tyr Gly Lys Tyr Ser Asp Gln Leu Ile	395	400	405
45	Val Asp Met Pro Thr Asp Asn Pro Glu Leu Asp Leu Phe Pro Glu	410	415	420
	Leu Ile Gly Thr Glu Glu Ile Ile Lys Glu Glu Glu Glu Gly Lys	425	430	435
50	Asp Ile Glu Glu Gly Ala Ile Val Asn Pro Gly Arg Asp Ser Ala	440	445	450
	Thr Asn Gln Ile Arg Lys Lys Glu Pro Gln Ile Ser Thr Thr Thr	455	460	465
55				

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	His Tyr Asn Arg Ile Gly Thr Lys Tyr Asn Glu Ala Lys Thr Asn	470	475	480
5	Arg Ser Pro Thr Arg Gly Ser Glu Phe Ser Gly Lys Gly Asp Val	485	490	495
	Pro Asn Thr Ser Leu Asn Ser Thr Ser Gln Pro Val Thr Lys Leu	500	505	510
10	Ala Thr Glu Lys Asp Ile Ser Leu Thr Ser Gln Thr Val Thr Glu	515	520	525
	Leu Pro Pro His Thr Val Glu Gly Thr Ser Ala Ser Leu Asn Asp	530	535	540
15	Gly Ser Lys Thr Val Leu Arg Ser Pro His Met Asn Leu Ser Gly	545	550	555
	Thr Ala Glu Ser Leu Asn Thr Val Ser Ile Thr Glu Tyr Glu Glu	560	565	570
20	Glu Ser Leu Leu Thr Ser Phe Lys Leu Asp Thr Gly Ala Glu Asp	575	580	585
	Ser Ser Gly Ser Ser Pro Ala Thr Ser Ala Ile Pro Phe Ile Ser	590	595	600
25	Glu Asn Ile Ser Gln Gly Tyr Ile Phe Ser Ser Glu Asn Pro Glu	605	610	615
	Thr Ile Thr Tyr Asp Val Leu Ile Pro Glu Ser Ala Arg Asn Ala	620	625	630
30	Ser Glu Asp Ser Thr Ser Ser Gly Ser Glu Glu Ser Leu Lys Asp	635	640	645
	Pro Ser Met Glu Gly Asn Val Trp Phe Pro Ser Ser Thr Asp Ile	650	655	660
35	Thr Ala Gln Pro Asp Val Gly Ser Gly Arg Glu Ser Phe Leu Gln	665	670	675
	Thr Asn Tyr Thr Glu Ile Arg Val Asp Glu Ser Glu Lys Thr Thr	680	685	690
40	Lys Ser Phe Ser Ala Gly Pro Val Met Ser Gln Gly Pro Ser Val	695	700	705
	Thr Asp Leu Glu Met Pro His Tyr Ser Thr Phe Ala Tyr Phe Pro	710	715	720
45	Thr Glu Val Thr Pro His Ala Phe Thr Pro Ser Ser Arg Gln Gln	725	730	735
50	Asp Leu Val Ser Thr Val Asn Val Val Tyr Ser Gln Thr Thr Gln	740	745	750
	Pro Val Tyr Asn Gly Glu Thr Pro Leu Gln Pro Ser Tyr Ser Ser	755	760	765
55	Glu Val Phe Pro Leu Val Thr Pro Leu Leu Leu Asp Asn Gln Ile			

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	770	775	780
5	Leu Asn Thr Thr Pro Ala Ala Ser Ser 785	Ser Asp Ser Ala Leu His 790	
	Ala Thr Pro Val Phe Pro Ser Val Asp 800	Val Ser Phe Glu Ser Ile 805	
10	Leu Ser Ser Tyr Asp Gly Ala Pro Leu 815	Leu Pro Phe Ser Ser Ala 820	
	Ser Phe Ser Ser Glu Leu Phe Arg His 830	Leu His Thr Val Ser Gln 835	
15	Ile Leu Pro Gln Val Thr Ser Ala Thr 845	Glu Ser Asp Lys Val Pro 850	
	Leu His Ala Ser Leu Pro Val Ala Gly 860	Gly Asp Leu Leu Leu Glu 865	
20	Pro Ser Leu Ala Gln Tyr Ser Asp Val 875	Leu Ser Thr Thr His Ala 880	
	Ala Ser Glu Thr Leu Glu Phe Gly Ser 890	Glu Ser Gly Val Leu Tyr 895	
25	Lys Thr Leu Met Phe Ser Gln Val Glu 905	Pro Pro Ser Ser Asp Ala 910	
	Met Met His Ala Arg Ser Ser Gly Pro 920	Glu Pro Ser Tyr Ala Leu 925	
30	Ser Asp Asn Glu Gly Ser Gln His Ile 935	Phe Thr Val Ser Tyr Ser 940	
	Ser Ala Ile Pro Val His Asp Ser Val 950	Gly Val Thr Tyr Gln Gly 955	
35	Ser Leu Phe Ser Gly Pro Ser His Ile 965	Pro Ile Pro Lys Ser Ser 970	
	Leu Ile Thr Pro Thr Ala Ser Leu Leu 980	Gln Pro Thr His Ala Leu 985	
40	Ser Gly Asp Gly Glu Trp Ser Gly Ala 995	Ser Ser Asp Ser Glu Phe 1000	
	Leu Leu Pro Asp Thr Asp Gly Leu Thr 1010	Ala Leu Asn Ile Ser Ser 1015	
45	Pro Val Ser Val Ala Glu Phe Thr Tyr 1025	Thr Thr Ser Val Phe Gly 1030	
	Asp Asp Asn Lys Ala Leu Ser Lys Ser 1040	Glu Ile Ile Tyr Gly Asn 1045	
50	Glu Thr Glu Leu Gln Ile Pro Ser Phe 1055	Asn Glu Met Val Tyr Pro 1060	
55	Ser Glu Ser Thr Val Met Pro Asn Met 1070	Tyr Asp Asn Val Asn Lys 1075	

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5	Leu Asn Ala Ser Leu Gln Glu Thr Ser Val Ser Ile Ser Ser Thr	1085	1090	1095
	Lys Gly Met Phe Pro Gly Ser Leu Ala His Thr Thr Thr Lys Val	1100	1105	1110
10	Phe Asp His Glu Ile Ser Gln Val Pro Glu Asn Asn Phe Ser Val	1115	1120	1125
	Gln Pro Thr His Thr Val Ser Gln Ala Ser Gly Asp Thr Ser Leu	1130	1135	1140
15	Lys Pro Val Leu Ser Ala Asn Ser Glu Pro Ala Ser Ser Asp Pro	1145	1150	1155
	Ala Ser Ser Glu Met Leu Ser Pro Ser Thr Gln Leu Leu Phe Tyr	1160	1165	1170
20	Glu Thr Ser Ala Ser Phe Ser Thr Glu Val Leu Leu Gln Pro Ser	1175	1180	1185
	Phe Gln Ala Ser Asp Val Asp Thr Leu Leu Lys Thr Val Leu Pro	1190	1195	1200
25	Ala Val Pro Ser Asp Pro Ile Leu Val Glu Thr Pro Lys Val Asp	1205	1210	1215
	Lys Ile Ser Ser Thr Met Leu His Leu Ile Val Ser Asn Ser Ala	1220	1225	1230
30	Ser Ser Glu Asn Met Leu His Ser Thr Ser Val Pro Val Phe Asp	1235	1240	1245
	Val Ser Pro Thr Ser His Met His Ser Ala Ser Leu Gln Gly Leu	1250	1255	1260
35	Thr Ile Ser Tyr Ala Ser Glu Lys Tyr Glu Pro Val Leu Leu Lys	1265	1270	1275
	Ser Glu Ser Ser His Gln Val Val Pro Ser Leu Tyr Ser Asn Asp	1280	1285	1290
40	Glu Leu Phe Gln Thr Ala Asn Leu Glu Ile Asn Gln Ala His Pro	1295	1300	1305
	Pro Lys Gly Arg His Val Phe Ala Thr Pro Val Leu Ser Ile Asp	1310	1315	1320
45	Glu Pro Leu Asn Thr Leu Ile Asn Lys Leu Ile His Ser Asp Glu	1325	1330	1335
	Ile Leu Thr Ser Thr Lys Ser Ser Val Thr Gly Lys Val Phe Ala	1340	1345	1350
50	Gly Ile Pro Thr Val Ala Ser Asp Thr Phe Val Ser Thr Asp His	1355	1360	1365
55	Ser Val Pro Ile Gly Asn Gly His Val Ala Ile Thr Ala Val Ser	1370	1375	1380

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	Pro His Arg Asp Gly Ser Val Thr Ser Thr Lys Leu Leu Phe Pro	
	1385	1390 1395
5	Ser Lys Ala Thr Ser Glu Leu Ser His Ser Ala Lys Ser Asp Ala	
	1400	1405 1410
	Gly Leu Val Gly Gly Gly Glu Asp Gly Asp Thr Asp Asp Asp Gly	
	1415	1420 1425
10	Asp Asp Asp Asp Asp Arg Asp Ser Asp Gly Leu Ser Ile His Lys	
	1430	1435 1440
	Cys Met Ser Cys Ser Ser Tyr Arg Glu Ser Gln Glu Lys Val Met	
	1445	1450 1455
15	Asn Asp Ser Asp Thr His Glu Asn Ser Leu Met Asp Gln Asn Asn	
	1460	1465 1470
	Pro Ile Ser Tyr Ser Leu Ser Glu Asn Ser Glu Glu Asp Asn Arg	
	1475	1480 1485
20	Val Thr Ser Val Ser Ser Asp Ser Gln Thr Gly Met Asp Arg Ser	
	1490	1495 1500
	Pro Gly Lys Ser Pro Ser Ala Asn Gly Leu Ser Gln Lys His Asn	
	1505	1510 1515
25	Asp Gly Lys Glu Glu Asn Asp Ile Gln Thr Gly Ser Ala Leu Leu	
	1520	1525 1530
	Pro Leu Ser Pro Glu Ser Lys Ala Trp Ala Val Leu Thr Ser Asp	
	1535	1540 1545
30	Glu Glu Ser Gly Ser Gly Gln Gly Thr Ser Asp Ser Leu Asn Glu	
	1550	1555 1560
	Asn Glu Thr Ser Thr Asp Phe Ser Phe Ala Asp Thr Asn Glu Lys	
	1565	1570 1575
35	Asp Ala Asp Gly Ile Leu Ala Ala Gly Asp Ser Glu Ile Thr Pro	
	1580	1585 1590
40	Gly Phe Pro Gln Ser Pro Thr Ser Ser Val Thr Ser Glu Asn Ser	
	1595	1600 1605
	Glu Val Phe His Val Ser Glu Ala Glu Ala Ser Asn Ser Ser His	
	1610	1615 1620
45	Glu Ser Arg Ile Gly Leu Ala Glu Gly Leu Glu Ser Glu Lys Lys	
	1625	1630 1635
	Ala Val Ile Pro Leu Val Ile Val Ser Ala Leu Thr Phe Ile Cys	
	1640	1645 1650
50	Leu Val Val Leu Val Gly Ile Leu Ile Tyr Trp Arg Lys Cys Phe	
	1655	1660 1665
	Gln Thr Ala His Phe Tyr Leu Glu Asp Ser Thr Ser Pro Arg Val	
	1670	1675 1680
55	Ile Ser Thr Pro Pro Thr Pro Ile Phe Pro Ile Ser Asp Asp Val	

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	1685	1690	1695
5	Gly Ala Ile Pro Ile Lys His Phe Pro Lys His Val Ala Asp Leu 1700	1705	1710
	His Ala Ser Ser Gly Phe Thr Glu Glu Phe Glu Thr Leu Lys Glu 1715	1720	1725
10	Phe Tyr Gln Glu Val Gln Ser Cys Thr Val Asp Leu Gly Ile Thr 1730	1735	1740
	Ala Asp Ser Ser Asn His Pro Asp Asn Lys His Lys Asn Arg Tyr 1745	1750	1755
15	Ile Asn Ile Val Ala Tyr Asp His Ser Arg Val Lys Leu Ala Gln 1760	1765	1770
	Leu Ala Glu Lys Asp Gly Lys Leu Thr Asp Tyr Ile Asn Ala Asn 1775	1780	1785
20	Tyr Val Asp Gly Tyr Asn Arg Pro Lys Ala Tyr Ile Ala Ala Gln 1790	1795	1800
	Gly Pro Leu Lys Ser Thr Ala Glu Asp Phe Trp Arg Met Ile Trp 1805	1810	1815
25	Glu His Asn Val Glu Val Ile Val Met Ile Thr Asn Leu Val Glu 1820	1825	1830
	Lys Gly Arg Arg Lys Cys Asp Gln Tyr Trp Pro Ala Asp Gly Ser 1835	1840	1845
30	Glu Glu Tyr Gly Asn Phe Leu Val Thr Gln Lys Ser Val Gln Val 1850	1855	1860
	Leu Ala Tyr Tyr Thr Val Arg Asn Phe Thr Leu Arg Asn Thr Lys 1865	1870	1875
35	Ile Lys Lys Gly Ser Gln Lys Gly Arg Pro Ser Gly Arg Val Val 1880	1885	1890
	Thr Gln Tyr His Tyr Thr Gln Trp Pro Asp Met Gly Val Pro Glu 1895	1900	1905
40	Tyr Ser Leu Pro Val Leu Thr Phe Val Arg Lys Ala Ala Tyr Ala 1910	1915	1920
	Lys Arg His Ala Val Gly Pro Val Val Val His Cys Ser Ala Gly 1925	1930	1935
45	Val Gly Arg Thr Gly Thr Tyr Ile Val Leu Asp Ser Met Leu Gln 1940	1945	1950
	Gln Ile Gln His Glu Gly Thr Val Asn Ile Phe Gly Phe Leu Lys 1955	1960	1965
50	His Ile Arg Ser Gln Arg Asn Tyr Leu Val Gln Thr Glu Glu Gln 1970	1975	1980
55	Tyr Val Phe Ile His Asp Thr Leu Val Glu Ala Ile Leu Ser Lys 1985	1990	1995

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5	Glu Thr Glu Val Leu Asp Ser His Ile His Ala Tyr Val Asn Ala	2000	2005	2010
	Leu Leu Ile Pro Gly Pro Ala Gly Lys Thr Lys Leu Glu Lys Gln	2015	2020	2025
10	Phe Gln Leu Leu Ser Gln Ser Asn Ile Gln Gln Ser Asp Tyr Ser	2030	2035	2040
	Ala Ala Leu Lys Gln Cys Asn Arg Glu Lys Asn Arg Thr Ser Ser	2045	2050	2055
15	Ile Ile Pro Val Glu Arg Ser Arg Val Gly Ile Ser Ser Leu Ser	2060	2065	2070
	Gly Glu Gly Thr Asp Tyr Ile Asn Ala Ser Tyr Ile Met Gly Tyr	2075	2080	2085
20	Tyr Gln Ser Asn Glu Phe Ile Ile Thr Gln His Pro Leu Leu His	2090	2095	2100
	Thr Ile Lys Asp Phe Trp Arg Met Ile Trp Asp His Asn Ala Gln	2105	2110	2115
25	Leu Val Val Met Ile Pro Asp Gly Gln Asn Met Ala Glu Asp Glu	2120	2125	2130
	Phe Val Tyr Trp Pro Asn Lys Asp Glu Pro Ile Asn Cys Glu Ser	2135	2140	2145
30	Phe Lys Val Thr Leu Met Ala Glu Glu His Lys Cys Leu Ser Asn	2150	2155	2160
	Glu Glu Lys Leu Ile Ile Gln Asp Phe Ile Leu Glu Ala Thr Gln	2165	2170	2175
35	Asp Asp Tyr Val Leu Glu Val Arg His Phe Gln Cys Pro Lys Trp	2180	2185	2190
	Pro Asn Pro Asp Ser Pro Ile Ser Lys Thr Phe Glu Leu Ile Ser	2195	2200	2205
40	Val Ile Lys Glu Glu Ala Ala Asn Arg Asp Gly Pro Met Ile Val	2210	2215	2220
	His Asp Glu His Gly Gly Val Thr Ala Gly Thr Phe Cys Ala Leu	2225	2230	2235
45	Thr Thr Leu Met His Gln Leu Glu Lys Glu Asn Ser Val Asp Val	2240	2245	2250
	Tyr Gln Val Ala Lys Met Ile Asn Leu Met Arg Pro Gly Val Phe	2255	2260	2265
50	Ala Asp Ile Glu Gln Tyr Gln Phe Leu Tyr Lys Val Ile Leu Ser	2270	2275	2280
	Leu Val Ser Thr Arg Gln Glu Glu Asn Pro Ser Thr Ser Leu Asp	2285	2290	2295
55				

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Ser Asn Gly Ala Ala Leu Pro Asp Gly Asn Ile Ala Glu Ser Leu
2300 2305 2310

5 Glu Ser Leu Val

<210> 111
<211> 774
10 <212> PRT
<213> Homo Sapien

<400> 111
Met Cys Ala Arg Met Ala Gly Arg Thr Arg Ala Ala Pro Arg Gly
1 5 10 15

15 Pro Tyr Gly Pro Trp Leu Cys Leu Leu Val Ala Leu Ala Leu Asp
20 25 30

Val Val Arg Val Asp Cys Gly Gln Ala Pro Leu Asp Pro Val Tyr
35 40 45

20 Leu His Val Thr Ala Ala Arg Pro Ala Gln Pro Thr Leu Trp Thr
50 55 60

Ala Lys Leu Asp Arg Phe Lys Gly Ser Arg His His Thr Thr Leu
65 70 75

25 Ile Thr Cys His Arg Ala Gly Leu Thr Glu Pro Asp Ser Ser Ser
80 85 90

Pro Leu Glu Leu Ser Glu Phe Leu Trp Val Asp Phe Val Val Glu
95 100 105

30 Asn Ser Thr Gly Gly Gly Val Ala Val Thr Arg Pro Val Thr Trp
110 115 120

Gln Leu Glu Tyr Pro Gly Gln Ala Pro Glu Ala Glu Lys Asp Lys
125 130 135

35 Met Val Trp Glu Ile Leu Val Ser Glu Arg Asp Ile Arg Ala Leu
140 145 150

Ile Pro Leu Ala Lys Ala Glu Glu Leu Val Asn Thr Ala Pro Leu
155 160 165

40 Thr Gly Val Pro Gln His Val Pro Val Arg Leu Val Thr Val Asp
170 175 180

Gly Gly Gly Ala Leu Val Glu Val Thr Glu His Val Gly Cys Glu
185 190 195

45 Ser Ala Asn Thr Gln Val Leu Gln Val Ser Glu Ala Cys Asp Ala
200 205 210

50 Val Phe Val Ala Gly Lys Glu Ser Arg Gly Ala Arg Gly Val Arg
215 220 225

Val Asp Phe Trp Trp Arg Arg Leu Arg Ala Ser Leu Arg Leu Thr
230 235 240

55 Val Trp Ala Pro Leu Leu Pro Leu Arg Ile Glu Leu Thr Asp Thr

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					245					250					255	
5		Thr	Leu	Glu	Gln	Val	Arg	Gly	Trp	Arg	Val	Pro	Gly	Pro	Ala	Glu
						260					265					270
		Gly	Pro	Ala	Glu	Pro	Ala	Ala	Glu	Ala	Ser	Asp	Glu	Ala	Glu	Arg
						275					280					285
10		Arg	Ala	Arg	Gly	Cys	His	Leu	Gln	Tyr	Gln	Arg	Ala	Gly	Val	Arg
						290					295					300
		Phe	Leu	Ala	Pro	Phe	Ala	Ala	His	Pro	Leu	Asp	Gly	Gly	Arg	Arg
						305					310					315
15		Leu	Thr	His	Leu	Leu	Gly	Pro	Asp	Trp	Leu	Leu	Asp	Val	Ser	His
						320					325					330
		Leu	Val	Ala	Pro	His	Ala	Arg	Val	Leu	Asp	Ser	Arg	Val	Ala	Ser
						335					340					345
20		Leu	Glu	Gly	Gly	Arg	Val	Val	Val	Gly	Arg	Glu	Pro	Gly	Val	Thr
						350					355					360
		Ser	Ile	Glu	Val	Arg	Ser	Pro	Leu	Ser	Asp	Ser	Ile	Leu	Gly	Glu
						365					370					375
25		Gln	Ala	Leu	Ala	Val	Thr	Asp	Asp	Lys	Val	Ser	Val	Leu	Glu	Leu
						380					385					390
		Arg	Val	Gln	Pro	Val	Met	Gly	Ile	Ser	Leu	Thr	Leu	Ser	Arg	Gly
						395					400					405
30		Thr	Ala	His	Pro	Gly	Glu	Val	Thr	Ala	Thr	Cys	Trp	Ala	Gln	Ser
						410					415					420
		Ala	Leu	Pro	Ala	Pro	Lys	Gln	Glu	Val	Ala	Leu	Ser	Leu	Trp	Leu
						425					430					435
35		Ser	Phe	Ser	Asp	His	Thr	Val	Ala	Pro	Ala	Glu	Leu	Tyr	Asp	Arg
						440					445					450
		Arg	Asp	Leu	Gly	Leu	Ser	Val	Ser	Ala	Glu	Glu	Pro	Gly	Ala	Ile
						455					460					465
40		Leu	Pro	Ala	Glu	Glu	Gln	Gly	Ala	Gln	Leu	Gly	Val	Val	Val	Ser
						470					475					480
		Gly	Ala	Gly	Ala	Glu	Gly	Leu	Pro	Leu	His	Val	Ala	Leu	His	Pro
						485					490					495
		Pro	Glu	Pro	Cys	Arg	Arg	Gly	Arg	His	Arg	Val	Pro	Leu	Ala	Ser
						500					505					510
50		Gly	Thr	Ala	Trp	Leu	Gly	Leu	Pro	Pro	Ala	Ser	Thr	Pro	Ala	Pro
						515					520					525
		Ala	Leu	Pro	Ser	Ser	Pro	Ala	Trp	Ser	Pro	Pro	Ala	Thr	Glu	Ala
						530					535					540
55		Thr	Met	Gly	Gly	Lys	Arg	Gln	Val	Ala	Gly	Ser	Val	Gly	Gly	Asn
						545					550					555

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5	Thr Gly Val Arg	Gly 560	Lys Phe Glu Arg	Ala 565	Glu Glu Glu Ala Arg	570
	Lys Glu Glu Thr	Glu 575	Ala Arg Glu Glu	Glu 580	Glu Glu Glu Glu Glu	585
10	Glu Met Val Pro	Ala 590	Pro Gln His Val	Thr 595	Glu Leu Glu Leu Gly	600
	Met Tyr Ala Leu	Leu 605	Gly Val Phe Cys	Val 610	Ala Ile Phe Ile Phe	615
15	Leu Val Asn Gly	Val 620	Val Phe Val Leu	Arg 625	Tyr Gln Arg Lys Glu	630
	Pro Pro Asp Ser	Ala 635	Thr Asp Pro Thr	Ser 640	Pro Gln Pro His Asn	645
20	Trp Val Trp Leu	Gly 650	Thr Asp Gln Glu	Glu 655	Leu Ser Arg Gln Leu	660
	Asp Arg Gln Ser	Pro 665	Gly Pro Pro Lys	Gly 670	Glu Gly Ser Cys Pro	675
25	Cys Glu Ser Gly	Gly 680	Gly Gly Glu Ala	Pro 685	Thr Leu Ala Pro Gly	690
	Pro Pro Gly Gly	Thr 695	Thr Ser Ser Ser	Ser 700	Thr Leu Ala Arg Lys	705
30	Glu Ala Gly Gly	Arg 710	Arg Lys Arg Val	Glu 715	Phe Val Thr Phe Val	720
	Pro Ala Pro Pro	Ala 725	Gln Ser Pro Glu	Glu 730	Pro Val Gly Ala Pro	735
35	Ala Val Gln Ser	Ile 740	Leu Val Ala Gly	Glu 745	Glu Asp Ile Arg Trp	750
	Val Cys Glu Asp	Met 755	Gly Leu Lys Asp	Pro 760	Glu Glu Leu Arg Asn	765
40	Tyr Met Glu Arg	Ile 770	Arg Gly Ser Ser			
45	<210> 112 <211> 420 <212> PRT <213> Homo Sapien					
50	<400> 112 Met Ala Thr Lys Thr Glu Leu Ser Pro Thr Ala Arg Glu Ser Lys 1 5 10 15					
	Asn Ala Gln Asp Met Gln Val Asp Glu Thr Leu Ile Pro Arg Lys 20 25 30					
55	Gly Pro Ser Leu Cys Ser Ala Arg Tyr Gly Ile Ala Leu Val Leu 35 40 45					

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	His	Phe	Cys	Asn	Phe	Thr	Thr	Ile	Ala	Gln	Asn	Val	Ile	Met	Asn	
					50					55					60	
5	Ile	Thr	Met	Val	Ala	Met	Val	Asn	Ser	Thr	Ser	Pro	Gln	Ser	Gln	
					65					70					75	
	Leu	Asn	Asp	Ser	Ser	Glu	Val	Leu	Pro	Val	Asp	Ser	Phe	Gly	Gly	
					80					85					90	
10	Leu	Ser	Lys	Ala	Pro	Lys	Ser	Leu	Pro	Ala	Lys	Ser	Ser	Ile	Leu	
					95					100					105	
	Gly	Gly	Gln	Phe	Ala	Ile	Trp	Glu	Lys	Trp	Gly	Pro	Pro	Gln	Glu	
					110					115					120	
15	Arg	Ser	Arg	Leu	Cys	Ser	Ile	Ala	Leu	Ser	Gly	Met	Leu	Leu	Gly	
					125					130					135	
	Cys	Phe	Thr	Ala	Ile	Leu	Ile	Gly	Gly	Phe	Ile	Ser	Glu	Thr	Leu	
					140					145					150	
20	Gly	Trp	Pro	Phe	Val	Phe	Tyr	Ile	Phe	Gly	Gly	Val	Gly	Cys	Val	
					155					160					165	
	Cys	Cys	Leu	Leu	Trp	Phe	Val	Val	Ile	Tyr	Asp	Asp	Pro	Phe	Ser	
					170					175					180	
25	Tyr	Pro	Trp	Ile	Ser	Thr	Ser	Glu	Lys	Glu	Tyr	Ile	Ile	Ser	Ser	
					185					190					195	
	Leu	Lys	Gln	Gln	Val	Gly	Ser	Ser	Lys	Gln	Pro	Leu	Pro	Ile	Lys	
					200					205					210	
	Ala	Met	Leu	Arg	Ser	Leu	Pro	Ile	Trp	Ser	Ile	Cys	Leu	Gly	Cys	
					215					220					225	
35	Phe	Ser	His	Gln	Trp	Leu	Val	Ser	Thr	Met	Val	Val	Tyr	Ile	Pro	
					230					235					240	
	Thr	Tyr	Ile	Ser	Ser	Val	Tyr	His	Val	Asn	Ile	Arg	Asp	Asn	Gly	
					245					250					255	
40	Leu	Leu	Ser	Ala	Leu	Pro	Phe	Ile	Val	Ala	Trp	Val	Ile	Gly	Met	
					260					265					270	
	Val	Gly	Gly	Tyr	Leu	Ala	Asp	Phe	Leu	Leu	Thr	Lys	Lys	Phe	Arg	
					275					280					285	
45	Leu	Ile	Thr	Val	Arg	Lys	Ile	Ala	Thr	Ile	Leu	Gly	Ser	Leu	Pro	
					290					295					300	
	Ser	Ser	Ala	Leu	Ile	Val	Ser	Leu	Pro	Tyr	Leu	Asn	Ser	Gly	Tyr	
					305					310					315	
50	Ile	Thr	Ala	Thr	Ala	Leu	Leu	Thr	Leu	Ser	Cys	Gly	Leu	Ser	Thr	
					320					325					330	
	Leu	Cys	Gln	Ser	Gly	Ile	Tyr	Ile	Asn	Val	Leu	Asp	Ile	Ala	Pro	
					335					340					345	
55	Arg	Tyr	Ser	Ser	Phe	Leu	Met	Gly	Ala	Ser	Arg	Gly	Phe	Ser	Ser	

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		350		355		360
5	Ile Ala Pro Val	Ile Val Pro Thr Val	Ser Gly Phe Leu Leu Ser			
		365	370			375
	Gln Asp Pro Glu	Phe Gly Trp Arg Asn Val	Phe Phe Leu Leu Phe			
		380	385			390
10	Ala Val Asn Leu	Leu Gly Leu Leu Phe Tyr	Leu Ile Phe Gly Glu			
		395	400			405
	Ala Asp Val Gln	Glu Trp Ala Lys Glu Arg	Lys Leu Thr Arg Leu			
		410	415			420
15	<210> 113					
	<211> 401					
	<212> PRT					
	<213> Homo Sapien					
20	<400> 113					
	Met Gln Val Asp	Glu Thr Leu Ile Pro Arg	Lys Val Pro Ser Leu			
	1	5	10			15
	Cys Ser Ala Arg	Tyr Gly Ile Ala Leu Val	Leu His Phe Cys Asn			
		20	25			30
25	Phe Thr Thr Ile	Ala Gln Asn Val Ile Met	Asn Ile Thr Met Val			
		35	40			45
	Ala Met Val Asn	Ser Thr Ser Pro Gln Ser	Gln Leu Asn Asp Ser			
		50	55			60
30	Ser Glu Val Leu	Pro Val Asp Ser Phe Gly	Gly Leu Ser Lys Ala			
		65	70			75
	Pro Lys Ser Leu	Pro Thr Lys Ser Ser Ile	Leu Gly Gly Gln Phe			
		80	85			90
35	Ala Ile Trp Glu	Lys Trp Gly Pro Pro Gln	Glu Arg Ser Arg Leu			
		95	100			105
	Cys Ser Ile Ala	Leu Ser Gly Met Leu Leu	Gly Cys Phe Thr Ala			
40		110	115			120
	Ile Leu Ile Gly	Gly Phe Ile Ser Glu Thr	Leu Gly Trp Pro Phe			
		125	130			135
	Val Phe Tyr Ile	Phe Gly Gly Val Gly Cys	Val Cys Cys Leu Leu			
45		140	145			150
	Trp Phe Val Val	Ile Tyr Asp Asp Pro Val	Ser Tyr Pro Trp Ile			
		155	160			165
	Ser Thr Ser Glu	Lys Glu Tyr Ile Ile Ser	Ser Ser Leu Lys Gln Gln			
50		170	175			180
	Val Arg Ser Ser	Lys Gln Pro Leu Pro Ile	Lys Ala Met Leu Arg			
		185	190			195
55	Ser Leu Pro Ile	Trp Ser Ile Cys Leu Gly	Cys Phe Ser His Gln			
		200	205			210

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5 Trp Leu Val Ser Thr Met Val Val Tyr Ile Pro Thr Tyr Ile Ser
 215 220 225
 Ser Val Tyr His Val Asn Ile Arg Asp Asn Gly Leu Leu Ser Ala
 230 235 240
 10 Leu Pro Phe Ile Val Ala Trp Val Ile Gly Met Val Gly Gly Tyr
 245 250 255
 Leu Ala Asp Phe Leu Leu Thr Lys Lys Phe Arg Leu Ile Thr Val
 260 265 270
 15 Arg Lys Ile Ala Thr Ile Leu Gly Ser Leu Pro Ser Ser Ala Leu
 275 280 285
 Ile Val Ser Leu Pro Tyr Leu Asn Ser Gly Tyr Ile Thr Ala Thr
 290 295 300
 20 Ala Leu Leu Thr Leu Ser Cys Gly Leu Ser Thr Leu Cys Gln Ser
 305 310 315
 Gly Ile Tyr Ile Asn Val Leu Asp Ile Ala Pro Arg Tyr Ser Ser
 320 325 330
 25 Phe Leu Met Gly Ala Ser Arg Gly Phe Ser Ser Ile Ala Pro Val
 335 340 345
 Ile Val Pro Thr Val Ser Gly Phe Leu Leu Ser Gln Asp Pro Glu
 350 355 360
 30 Phe Gly Trp Arg Asn Val Phe Phe Leu Leu Phe Ala Val Asn Leu
 365 370 375
 Leu Gly Leu Leu Phe Tyr Leu Ile Phe Gly Glu Ala Asp Val Gln
 380 385 390
 35 Glu Trp Ala Lys Glu Arg Lys Leu Thr Arg Leu
 395 400
 <210> 114
 <211> 507
 <212> PRT
 40 <213> Homo Sapien
 <400> 114
 Met Ala Gly Ala Gly Pro Lys Arg Arg Ala Leu Ala Ala Pro Ala
 1 5 10 15
 45 Ala Glu Glu Lys Glu Glu Ala Arg Glu Lys Met Leu Ala Ala Lys
 20 25 30
 Ser Ala Asp Gly Ser Ala Pro Ala Gly Glu Gly Glu Gly Val Thr
 35 40 45
 50 Leu Gln Arg Asn Ile Thr Leu Leu Asn Gly Val Ala Ile Ile Val
 50 55 60
 Gly Thr Ile Ile Gly Ser Gly Ile Phe Val Thr Pro Thr Gly Val
 65 70 75
 55

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	Leu	Lys	Glu	Ala	Gly	Ser	Pro	Gly	Leu	Ala	Leu	Val	Val	Trp	Ala	
					80					85					90	
5	Ala	Cys	Gly	Val	Phe	Ser	Ile	Val	Gly	Ala	Leu	Cys	Tyr	Ala	Glu	
					95					100					105	
	Leu	Gly	Thr	Thr	Ile	Ser	Lys	Ser	Gly	Gly	Asp	Tyr	Ala	Tyr	Met	
					110					115					120	
10	Leu	Glu	Val	Tyr	Gly	Ser	Leu	Pro	Ala	Phe	Leu	Lys	Leu	Trp	Ile	
					125					130					135	
	Glu	Leu	Leu	Ile	Ile	Arg	Pro	Ser	Ser	Gln	Tyr	Ile	Val	Ala	Leu	
					140					145					150	
15	Val	Phe	Ala	Thr	Tyr	Leu	Leu	Lys	Pro	Leu	Phe	Pro	Thr	Cys	Pro	
					155					160					165	
	Val	Pro	Glu	Glu	Ala	Ala	Lys	Leu	Val	Ala	Cys	Leu	Cys	Val	Leu	
20					170					175					180	
	Leu	Leu	Thr	Ala	Val	Asn	Cys	Tyr	Ser	Val	Lys	Ala	Ala	Thr	Arg	
					185					190					195	
	Val	Gln	Asp	Ala	Phe	Ala	Ala	Ala	Lys	Leu	Leu	Ala	Leu	Ala	Leu	
25					200					205					210	
	Ile	Ile	Leu	Leu	Gly	Phe	Val	Gln	Ile	Gly	Lys	Gly	Asp	Val	Ser	
					215					220					225	
	Asn	Leu	Asp	Pro	Lys	Phe	Ser	Phe	Glu	Gly	Thr	Lys	Leu	Asp	Val	
30					230					235					240	
	Gly	Asn	Ile	Val	Leu	Ala	Leu	Tyr	Ser	Gly	Leu	Phe	Ala	Tyr	Gly	
					245					250					255	
	Gly	Trp	Asn	Tyr	Leu	Asn	Phe	Val	Thr	Glu	Glu	Met	Ile	Asn	Pro	
35					260					265					270	
	Tyr	Arg	Asn	Leu	Pro	Leu	Ala	Ile	Ile	Ile	Ser	Leu	Pro	Ile	Val	
					275					280					285	
40	Thr	Leu	Val	Tyr	Val	Leu	Thr	Asn	Leu	Ala	Tyr	Phe	Thr	Thr	Leu	
					290					295					300	
	Ser	Thr	Glu	Gln	Met	Leu	Ser	Ser	Glu	Ala	Val	Ala	Val	Asp	Phe	
					305					310					315	
45	Gly	Asn	Tyr	His	Leu	Gly	Val	Met	Ser	Trp	Ile	Ile	Pro	Val	Phe	
					320					325					330	
	Val	Gly	Leu	Ser	Cys	Phe	Gly	Ser	Val	Asn	Gly	Ser	Leu	Phe	Thr	
					335					340					345	
50	Ser	Ser	Arg	Leu	Phe	Phe	Val	Gly	Ser	Arg	Glu	Gly	His	Leu	Pro	
					350					355					360	
	Ser	Ile	Leu	Ser	Met	Ile	His	Pro	Gln	Leu	Leu	Thr	Pro	Val	Pro	
					365					370					375	
55	Ser	Leu	Val	Phe	Thr	Cys	Val	Met	Thr	Leu	Leu	Tyr	Ala	Phe	Ser	

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	380	385	390
5	Lys Asp Ile Phe Ser Val Ile Asn Phe	Phe Ser Phe Phe Asn Trp	
	395	400	405
	Leu Cys Val Ala Leu Ala Ile Ile Gly	Met Ile Trp Leu Arg His	
	410	415	420
10	Arg Lys Pro Glu Leu Glu Arg Pro Ile	Lys Val Asn Leu Ala Leu	
	425	430	435
	Pro Val Phe Phe Ile Leu Ala Cys Leu	Phe Leu Ile Ala Val Ser	
	440	445	450
15	Phe Trp Lys Thr Pro Val Glu Cys Gly	Ile Gly Phe Thr Ile Ile	
	455	460	465
	Leu Ser Gly Leu Pro Val Tyr Phe Phe	Gly Val Trp Trp Lys Asn	
	470	475	480
20	Lys Pro Lys Trp Leu Leu Gln Gly Ile	Phe Ser Thr Thr Val Leu	
	485	490	495
	Cys Gln Lys Leu Met Gln Val Val Pro	Gln Glu Thr	
	500	505	
25	<210> 115		
	<211> 507		
	<212> PRT		
	<213> Homo Sapien		
30	<400> 115		
	Met Ala Gly Ala Gly Pro Lys Arg Arg	Ala Leu Ala Ala Pro Ala	
	1	5	10 15
	Ala Glu Glu Lys Glu Glu Ala Arg Glu	Lys Met Leu Ala Ala Lys	
	20	25	30
35	Ser Ala Asp Gly Ser Ala Pro Ala Gly	Glu Gly Glu Gly Val Thr	
	35	40	45
	Leu Gln Arg Asn Ile Thr Leu Leu Asn	Gly Val Ala Ile Ile Val	
	50	55	60
40	Gly Thr Ile Ile Gly Ser Gly Ile Phe	Val Thr Pro Thr Gly Val	
	65	70	75
	Leu Lys Glu Ala Gly Ser Pro Gly Leu	Ala Leu Val Val Trp Ala	
	80	85	90
45	Ala Cys Gly Val Phe Ser Ile Val Gly	Ala Leu Cys Tyr Ala Glu	
	95	100	105
	Leu Gly Thr Thr Ile Ser Lys Ser Gly	Gly Asp Tyr Ala Tyr Met	
	110	115	120
50	Leu Glu Val Tyr Gly Ser Leu Pro Ala	Phe Leu Lys Leu Trp Ile	
	125	130	135
55	Glu Leu Leu Ile Ile Arg Pro Ser Ser	Gln Tyr Ile Val Ala Leu	
	140	145	150

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5	Val	Phe	Ala	Thr	Tyr	Leu	Leu	Lys	Pro	Leu	Phe	Pro	Thr	Cys	Pro	
					155					160					165	
	Val	Pro	Glu	Glu	Ala	Ala	Lys	Leu	Val	Ala	Cys	Leu	Cys	Val	Leu	
					170					175					180	
10	Leu	Leu	Thr	Ala	Val	Asn	Cys	Tyr	Ser	Val	Lys	Ala	Ala	Thr	Arg	
					185					190					195	
	Val	Gln	Asp	Ala	Phe	Ala	Ala	Ala	Lys	Leu	Leu	Ala	Leu	Ala	Leu	
					200					205					210	
15	Ile	Ile	Leu	Leu	Gly	Phe	Val	Gln	Ile	Gly	Lys	Gly	Asp	Val	Ser	
					215					220					225	
	Asn	Leu	Asp	Pro	Asn	Phe	Ser	Phe	Glu	Gly	Thr	Lys	Leu	Asp	Val	
					230					235					240	
20	Gly	Asn	Ile	Val	Leu	Ala	Leu	Tyr	Ser	Gly	Leu	Phe	Ala	Tyr	Gly	
					245					250					255	
	Gly	Trp	Asn	Tyr	Leu	Asn	Phe	Val	Thr	Glu	Glu	Met	Ile	Asn	Pro	
					260					265					270	
25	Tyr	Arg	Asn	Leu	Pro	Leu	Ala	Ile	Ile	Ile	Ser	Leu	Pro	Ile	Val	
					275					280					285	
	Thr	Leu	Val	Tyr	Val	Leu	Thr	Asn	Leu	Ala	Tyr	Phe	Thr	Thr	Leu	
					290					295					300	
30	Ser	Thr	Glu	Gln	Met	Leu	Ser	Ser	Glu	Ala	Val	Ala	Val	Asp	Phe	
					305					310					315	
	Gly	Asn	Tyr	His	Leu	Gly	Val	Met	Ser	Trp	Ile	Ile	Pro	Val	Phe	
					320					325					330	
35	Val	Gly	Leu	Ser	Cys	Phe	Gly	Ser	Val	Asn	Gly	Ser	Leu	Phe	Thr	
					335					340					345	
	Ser	Ser	Arg	Leu	Phe	Phe	Val	Gly	Ser	Arg	Glu	Gly	His	Leu	Pro	
					350					355					360	
40	Ser	Ile	Leu	Ser	Met	Ile	His	Pro	Gln	Leu	Leu	Thr	Pro	Val	Pro	
					365					370					375	
	Ser	Leu	Val	Phe	Thr	Cys	Val	Met	Thr	Leu	Leu	Tyr	Ala	Phe	Ser	
					380					385					390	
45	Lys	Asp	Ile	Phe	Ser	Val	Ile	Asn	Phe	Phe	Ser	Phe	Phe	Asn	Trp	
					395					400					405	
	Leu	Cys	Val	Ala	Leu	Ala	Ile	Ile	Gly	Met	Ile	Trp	Leu	Arg	His	
					410					415					420	
50	Arg	Lys	Pro	Glu	Leu	Glu	Arg	Pro	Ile	Lys	Val	Asn	Leu	Ala	Leu	
					425					430					435	
	Pro	Val	Phe	Phe	Ile	Leu	Ala	Cys	Leu	Phe	Leu	Ile	Ala	Val	Ser	
55					440					445					450	

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	Phe Trp Lys Thr Pro Val Glu Cys Gly Ile Gly Phe Thr Ile Ile	455	460	465
5	Leu Ser Gly Leu Pro Val Tyr Phe Phe Gly Val Trp Trp Lys Asn	470	475	480
	Lys Pro Lys Trp Leu Leu Gln Gly Ile Phe Ser Thr Thr Val Leu	485	490	495
10	Cys Gln Lys Leu Met Gln Val Val Pro Gln Glu Thr	500	505	
	<210> 116			
	<211> 622			
15	<212> PRT			
	<213> Homo Sapien			
	<400> 116			
	Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr	1	5	10 15
20	Pro Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp	20	25	30
	Val Gln Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala	35	40	45
25	Ala Pro Leu Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser	50	55	60
	Leu Ser Pro Arg Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser	65	70	75
30	Gly Leu Ser Thr Glu Arg Val Arg Glu Leu Ala Val Ala Leu Ala	80	85	90
	Gln Lys Asn Val Lys Leu Ser Thr Glu Gln Leu Arg Cys Leu Ala	95	100	105
35	His Arg Leu Ser Glu Pro Pro Glu Asp Leu Asp Ala Leu Pro Leu	110	115	120
	Asp Leu Leu Leu Phe Leu Asn Pro Asp Ala Phe Ser Gly Pro Gln	125	130	135
40	Ala Cys Thr Arg Phe Phe Ser Arg Ile Thr Lys Ala Asn Val Asp	140	145	150
	Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln Arg Leu Leu Pro Ala	155	160	165
45	Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu Leu Ser Glu Ala	170	175	180
	Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu Pro Gly Arg	185	190	195
50	Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu Val Ser	200	205	210
55	Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg Ala			

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					215						220					225
5		Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp
					230						235					240
		Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu
					245						250					255
10		Gly	Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala
					260						265					270
		Trp	Arg	Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu
					275						280					285
15		Arg	Thr	Ile	Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr
					290						295					300
		Ala	Cys	Pro	Ser	Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu
					305						310					315
20		Ile	Phe	Tyr	Lys	Lys	Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala
					320						325					330
		Leu	Leu	Ala	Thr	Gln	Met	Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr
					335						340					345
25		Tyr	Glu	Gln	Leu	Asp	Val	Leu	Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr
					350						355					360
		Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	Ile	Gln	His	Leu	Gly	Tyr	Leu
					365						370					375
30		Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	Arg	Lys	Trp	Asn	Val	Thr
					380						385					390
		Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	Val	Asn	Lys	Gly	His
					395						400					405
35		Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys
					410						415					420
		Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala
40					425						430					435
		Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser
					440						445					450
		Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu
45					455						460					465
		Asp	Thr	Cys	Asp	Pro	Arg	Gln	Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala
					470						475					480
		Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	Gly	Ser	Glu	Tyr	Phe	Val	Lys
50					485						490					495
		Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro	Thr	Glu	Asp	Leu	Lys	Ala
					500						505					510
55		Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	Ala	Thr	Phe	Met	Lys
					515						520					525

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5	Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln	530	535	540
	Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg	545	550	555
10	His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp	560	565	570
	Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn Gly	575	580	585
15	Tyr Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr	590	595	600
	Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu	605	610	615
20	Leu Leu Ala Ser Thr Leu Ala	620		
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25	<213> Homo Sapien			
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	Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro	1	5	10
30	Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val	20	25	30
	Gln Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala	35	40	45
35	Pro Leu Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu	50	55	60
	Ser Pro Arg Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly	65	70	75
40	Leu Ser Thr Glu Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln	80	85	90
	Lys Asn Val Lys Leu Ser Thr Glu Gln Leu Arg Cys Leu Ala His	95	100	105
45	Arg Leu Ser Glu Pro Pro Glu Asp Leu Asp Ala Leu Pro Leu Asp	110	115	120
	Leu Leu Leu Phe Leu Asn Pro Asp Ala Phe Ser Gly Pro Gln Ala	125	130	135
50	Cys Thr Arg Phe Phe Ser Arg Ile Thr Lys Ala Asn Val Asp Leu	140	145	150
	Leu Pro Arg Gly Ala Pro Glu Arg Gln Arg Leu Leu Pro Ala Ala	155	160	165
55				

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	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu	Leu	Ser	Glu	Ala	Asp
					170					175					180
5	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	Pro	Gly	Arg	Phe
					185					190					195
	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	Val	Ser	Cys
					200					205					210
10	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	Ala	Ala
					215					220					225
	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	Ser
					230					235					240
15	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
					245					250					255
	Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp
					260					265					270
20	Arg	Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg
					275					280					285
	Thr	Ile	Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala
25					290					295					300
	Cys	Pro	Ser	Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile
					305					310					315
	Phe	Tyr	Lys	Lys	Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu
30					320					325					330
	Leu	Ala	Thr	Gln	Met	Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr
					335					340					345
	Glu	Gln	Leu	Asp	Val	Leu	Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro
35					350					355					360
	Gln	Gly	Tyr	Pro	Glu	Ser	Val	Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe
					365					370					375
	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	Arg	Lys	Trp	Asn	Val	Thr	Ser
40					380					385					390
	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	Val	Asn	Lys	Gly	His	Glu
					395					400					405
	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly
45					410					415					420
	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe
					425					430					435
	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser
50					440					445					450
	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp
					455					460					465
55	Thr	Cys	Asp	Pro	Arg	Gln	Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg

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		470		475		480
5	Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile	485		490		495
	Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu	500		505		510
10	Ser Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu	515		520		525
	Arg Thr Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys	530		535		540
15	Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His	545		550		555
	Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu	560		565		570
20	Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr	575		580		585
	Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr Pro	590		595		600
25	Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu	605		610		615
	Leu Ala Ser Thr Leu Ala	620				
30	<210> 118 <211> 357 <212> PRT <213> Homo Sapien					
35	<400> 118					
	Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser	1	5	10		15
40	Lys Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val	20		25		30
	Leu Glu Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe	35		40		45
45	Met Leu Thr Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn	50		55		60
	Arg Arg Lys Met Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val	65		70		75
50	Leu Gly Ile Phe Gly Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp	80		85		90
	Gly Ser Thr Gly Pro Thr Arg Phe Phe Leu Phe Gly Ile Leu Phe	95		100		105
55	Ser Ile Cys Phe Ser Cys Leu Leu Ala His Ala Val Ser Leu Thr	110		115		120

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5	Lys Leu Val Arg Gly Arg Lys Pro Leu Ser Leu Leu Val Ile Leu	125	130	135																												
	Gly Leu Ala Val Gly Phe Ser Leu Val Gln Asp Val Ile Ala Ile	140	145	150																												
10	Glu Tyr Ile Val Leu Thr Met Asn Arg Thr Asn Val Asn Val Phe	155	160	165																												
	Ser Glu Leu Ser Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu	170	175	180																												
15	Leu Thr Tyr Val Leu Phe Leu Met Ala Leu Thr Phe Leu Met Ser	185	190	195																												
	Ser Phe Thr Phe Cys Gly Ser Phe Thr Gly Trp Lys Arg His Gly	200	205	210																												
20	Ala His Ile Tyr Leu Thr Met Leu Leu Ser Ile Ala Ile Trp Val	215	220	225																												
	Ala Trp Ile Thr Leu Leu Met Leu Pro Asp Phe Asp Arg Arg Trp	230	235	240																												
25	Asp Asp Thr Ile Leu Ser Ser Ala Leu Ala Ala Asn Gly Trp Val	245	250	255																												
	Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe Trp Leu Leu Thr Lys	260	265	270																												
30	Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp Ala Phe Cys Lys	275	280	285																												
	Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn Arg Ala Tyr	290	295	300																												
35	Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly Asp Thr	305	310	315																												
	Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln Pro	320	325	330																												
40	Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser	335	340	345																												
	Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser	350	355																													
45	<210> 119 <211> 836 <212> PRT <213> Homo Sapien																															
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Met	Ile	Pro	Phe	Leu	Pro	Met	Phe	Ser	Leu	Leu	Leu	Leu	Ile																			
1				5					10				15																			
55	Val	Asn	Pro	Ile	Asn	Ala	Asn	Asn	His	Tyr	Asp	Lys	Ile	Leu	Ala																	
					20					25					30																	

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	His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala	35	40	45
5	Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys	50	55	60
	Lys Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val	65	70	75
10	Leu Tyr Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys	80	85	90
	Gly Cys Pro Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu	95	100	105
15	Gly Ile Val Gly Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser	110	115	120
	Lys Leu Arg Glu Glu Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe	125	130	135
20	Ala Pro Ser Asn Glu Ala Trp Asp Asn Leu Asp Ser Asp Ile Arg	140	145	150
	Arg Gly Leu Glu Ser Asn Val Asn Val Glu Leu Leu Asn Ala Leu	155	160	165
25	His Ser His Met Ile Asn Lys Arg Met Leu Thr Lys Asp Leu Lys	170	175	180
	Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu Gly Leu Phe	185	190	195
30	Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys Ala Arg	200	205	210
	Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His Val	215	220	225
35	Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe	230	235	240
	Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile	245	250	255
40	Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr	260	265	270
	Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly	275	280	285
45	Val Leu Glu Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu	290	295	300
	Met Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile	305	310	315
50	Met Gly Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu	320	325	330
55	Ile Gly Cys Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met			

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		335		340		345
5	Val Asn Lys Lys Asp Ile Val Thr Asn Asn Gly Val Ile His Leu	350		355		360
	Ile Asp Gln Val Leu Ile Pro Asp Ser Ala Lys Gln Val Ile Glu	365		370		375
10	Leu Ala Gly Lys Gln Gln Thr Thr Phe Thr Asp Leu Val Ala Gln	380		385		390
	Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp Gly Glu Tyr Thr Leu	395		400		405
15	Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp Thr Leu Ser Met	410		415		420
	Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His Ile Leu Lys	425		430		435
20	Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile Leu Glu	440		445		450
	Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr Ala	455		460		465
25	Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly	470		475		480
	Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala	485		490		495
30	Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser	500		505		510
	Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu	515		520		525
35	Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala	530		535		540
	Phe Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp	545		550		555
40	Lys Asn Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly	560		565		570
	Val Phe Ile Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu	575		580		585
45	Lys Thr Thr Gln Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp	590		595		600
	Thr Leu Leu Val Asn Glu Leu Lys Ser Lys Glu Ser Asp Ile Met	605		610		615
50	Thr Thr Asn Gly Val Ile His Val Val Asp Lys Leu Leu Tyr Pro	620		625		630
55	Ala Asp Thr Pro Val Gly Asn Asp Gln Leu Leu Glu Ile Leu Asn	635		640		645

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5	Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val Arg Gly Ser Thr	650	655	660
	Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys Ile Ile Thr	665	670	675
10	Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser Leu Gln	680	685	690
	Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys Ile	695	700	705
15	Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile	710	715	720
	Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys	725	730	735
20	Ile Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg	740	745	750
	Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile	755	760	765
25	Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu	770	775	780
	Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp	785	790	795
30	Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly	800	805	810
	Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly	815	820	825
35	Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln	830	835	
40	<210> 120			
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45	<400> 120			
	Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile	1	5	10
				15
50	Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala	20	25	30
	His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala	35	40	45
	Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys	50	55	60
55	Lys Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val	65	70	75

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	Leu Tyr Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys	80	85	90
5	Gly Cys Pro Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu	95	100	105
	Gly Ile Val Gly Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser	110	115	120
10	Lys Leu Arg Glu Glu Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe	125	130	135
	Ala Pro Ser Asn Glu Ala Trp Asp Asn Leu Asp Ser Asp Ile Arg	140	145	150
15	Arg Gly Leu Glu Ser Asn Val Asn Val Glu Leu Leu Asn Ala Leu	155	160	165
	His Ser His Met Ile Asn Lys Arg Met Leu Thr Lys Asp Leu Lys	170	175	180
20	Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu Gly Leu Phe	185	190	195
	Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys Ala Arg	200	205	210
25	Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His Val	215	220	225
	Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe	230	235	240
30	Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile	245	250	255
	Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr	260	265	270
35	Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly	275	280	285
	Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu	290	295	300
40	Met Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile	305	310	315
	Met Gly Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu	320	325	330
45	Ile Gly Cys Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met	335	340	345
	Val Asn Lys Lys Asp Ile Val Thr Asn Asn Gly Val Ile His Leu	350	355	360
50	Ile Asp Gln Val Leu Ile Pro Asp Ser Ala Lys Gln Val Ile Glu	365	370	375
55	Leu Ala Gly Lys Gln Gln Thr Thr Phe Thr Asp Leu Val Ala Gln			

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					380					385					390
5	Leu	Gly	Leu	Ala	Ser	Ala	Leu	Arg	Pro	Asp	Gly	Glu	Tyr	Thr	Leu
					395					400					405
	Leu	Ala	Pro	Val	Asn	Asn	Ala	Phe	Ser	Asp	Asp	Thr	Leu	Ser	Met
					410					415					420
10	Asp	Gln	Arg	Leu	Leu	Lys	Leu	Ile	Leu	Gln	Asn	His	Ile	Leu	Lys
					425					430					435
	Val	Lys	Val	Gly	Leu	Asn	Glu	Leu	Tyr	Asn	Gly	Gln	Ile	Leu	Glu
					440					445					450
15	Thr	Ile	Gly	Gly	Lys	Gln	Leu	Arg	Val	Phe	Val	Tyr	Arg	Thr	Ala
					455					460					465
	Val	Cys	Ile	Glu	Asn	Ser	Cys	Met	Glu	Lys	Gly	Ser	Lys	Gln	Gly
					470					475					480
20	Arg	Asn	Gly	Ala	Ile	His	Ile	Phe	Arg	Glu	Ile	Ile	Lys	Pro	Ala
					485					490					495
	Glu	Lys	Ser	Leu	His	Glu	Lys	Leu	Lys	Gln	Asp	Lys	Arg	Phe	Ser
					500					505					510
25	Thr	Phe	Leu	Ser	Leu	Leu	Glu	Ala	Ala	Asp	Leu	Lys	Glu	Leu	Leu
					515					520					525
	Thr	Gln	Pro	Gly	Asp	Trp	Thr	Leu	Phe	Val	Pro	Thr	Asn	Asp	Ala
					530					535					540
30	Phe	Lys	Gly	Met	Thr	Ser	Glu	Glu	Lys	Glu	Ile	Leu	Ile	Arg	Asp
					545					550					555
	Lys	Asn	Ala	Leu	Gln	Asn	Ile	Ile	Leu	Tyr	His	Leu	Thr	Pro	Gly
					560					565					570
35	Val	Phe	Ile	Gly	Lys	Gly	Phe	Glu	Pro	Gly	Val	Thr	Asn	Ile	Leu
					575					580					585
	Lys	Thr	Thr	Gln	Gly	Ser	Lys	Ile	Phe	Leu	Lys	Glu	Val	Asn	Asp
					590					595					600
40	Thr	Leu	Leu	Val	Asn	Glu	Leu	Lys	Ser	Lys	Glu	Ser	Asp	Ile	Met
					605					610					615
	Thr	Thr	Asn	Gly	Val	Ile	His	Val	Val	Asp	Lys	Leu	Leu	Tyr	Pro
45					620					625					630
	Ala	Asp	Thr	Pro	Val	Gly	Asn	Asp	Gln	Leu	Leu	Glu	Ile	Leu	Asn
					635					640					645
50	Lys	Leu	Ile	Lys	Tyr	Ile	Gln	Ile	Lys	Phe	Val	Arg	Gly	Ser	Thr
					650					655					660
	Phe	Lys	Glu	Ile	Pro	Val	Thr	Val	Tyr	Arg	Pro	Thr	Leu	Thr	Lys
					665					670					675
55	Val	Lys	Ile	Glu	Gly	Glu	Pro	Glu	Phe	Arg	Leu	Ile	Lys	Glu	Gly
					680					685					690

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5	Glu Thr Ile Thr	Glu Val Ile His Gly	Glu Pro Ile Ile Lys Lys
	695		700 705
	Tyr Thr Lys Ile	Ile Asp Gly Val Pro	Val Glu Ile Thr Glu Lys
	710		715 720
10	Glu Thr Arg Glu	Glu Arg Ile Ile Thr	Gly Pro Glu Ile Lys Tyr
	725		730 735
	Thr Arg Ile Ser	Thr Gly Gly Gly Glu	Thr Glu Glu Thr Leu Lys
	740		745 750
15	Lys Leu Leu Gln	Glu Glu Val Thr Lys	Val Thr Lys Phe Ile Glu
	755		760 765
	Gly Gly Asp Gly	His Leu Phe Glu Asp	Glu Glu Ile Lys Arg Leu
	770		775 780
20	Leu Gln Gly Asp	Thr Pro Val Arg Lys	Leu Gln Ala Asn Lys Lys
	785		790 795
	Val Gln Gly Ser	Arg Arg Arg Leu Arg	Glu Gly Arg Ser Gln
	800		805
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	<212> PRT		
	<213> Homo Sapien		
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	1	5	10 15
	Val Asn Pro Ile	Asn Ala Asn Asn His	Tyr Asp Lys Ile Leu Ala
		20	25 30
35	His Ser Arg Ile	Arg Gly Arg Asp Gln	Gly Pro Asn Val Cys Ala
		35	40 45
	Leu Gln Gln Ile	Leu Gly Thr Lys Lys	Lys Tyr Phe Ser Thr Cys
		50	55 60
40	Lys Asn Trp Tyr	Lys Lys Ser Ile Cys	Gly Gln Lys Thr Thr Val
		65	70 75
	Leu Tyr Glu Cys	Cys Pro Gly Tyr Met	Arg Met Glu Gly Met Lys
		80	85 90
45	Gly Cys Pro Ala	Val Leu Pro Ile Asp	His Val Tyr Gly Thr Leu
		95	100 105
	Gly Ile Val Gly	Ala Thr Thr Thr Gln	Arg Tyr Ser Asp Ala Ser
		110	115 120
50	Lys Leu Arg Glu	Glu Ile Glu Gly Lys	Gly Ser Phe Thr Tyr Phe
		125	130 135
55	Ala Pro Ser Asn	Glu Ala Trp Asp Asn	Leu Asp Ser Asp Ile Arg
		140	145 150

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	Arg	Gly	Leu	Glu	Ser	Asn	Val	Asn	Val	Glu	Leu	Leu	Asn	Ala	Leu	
					155					160					165	
5	His	Ser	His	Met	Ile	Asn	Lys	Arg	Met	Leu	Thr	Lys	Asp	Leu	Lys	
					170					175					180	
	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu	Gly	Leu	Phe	
					185					190					195	
10	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys	Ala	Arg	
					200					205					210	
	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His	Val	
					215					220					225	
15	Ile	Asp	Arg	Val	Leu	Thr	Gln	Ile	Gly	Thr	Ser	Ile	Gln	Asp	Phe	
					230					235					240	
	Ile	Glu	Ala	Glu	Asp	Asp	Leu	Ser	Ser	Phe	Arg	Ala	Ala	Ala	Ile	
20					245					250					255	
	Thr	Ser	Asp	Ile	Leu	Glu	Ala	Leu	Gly	Arg	Asp	Gly	His	Phe	Thr	
					260					265					270	
	Leu	Phe	Ala	Pro	Thr	Asn	Glu	Ala	Phe	Glu	Lys	Leu	Pro	Arg	Gly	
25					275					280					285	
	Val	Leu	Glu	Arg	Ile	Met	Gly	Asp	Lys	Val	Ala	Ser	Glu	Ala	Leu	
					290					295					300	
	Met	Lys	Tyr	His	Ile	Leu	Asn	Thr	Leu	Gln	Cys	Ser	Glu	Ser	Ile	
30					305					310					315	
	Met	Gly	Gly	Ala	Val	Phe	Glu	Thr	Leu	Glu	Gly	Asn	Thr	Ile	Glu	
					320					325					330	
	Ile	Gly	Cys	Asp	Gly	Asp	Ser	Ile	Thr	Val	Asn	Gly	Ile	Lys	Met	
35					335					340					345	
	Val	Asn	Lys	Lys	Asp	Ile	Val	Thr	Asn	Asn	Gly	Val	Ile	His	Leu	
					350					355					360	
	Ile	Asp	Gln	Val	Leu	Ile	Pro	Asp	Ser	Ala	Lys	Gln	Val	Ile	Glu	
40					365					370					375	
	Leu	Ala	Gly	Lys	Gln	Gln	Thr	Thr	Phe	Thr	Asp	Leu	Val	Ala	Gln	
					380					385					390	
	Leu	Gly	Leu	Ala	Ser	Ala	Leu	Arg	Pro	Asp	Gly	Glu	Tyr	Thr	Leu	
45					395					400					405	
	Leu	Ala	Pro	Val	Asn	Asn	Ala	Phe	Ser	Asp	Asp	Thr	Leu	Ser	Met	
					410					415					420	
	Asp	Gln	Arg	Leu	Leu	Lys	Leu	Ile	Leu	Gln	Asn	His	Ile	Leu	Lys	
50					425					430					435	
	Val	Lys	Val	Gly	Leu	Asn	Glu	Leu	Tyr	Asn	Gly	Gln	Ile	Leu	Glu	
					440					445					450	
55	Thr	Ile	Gly	Gly	Lys	Gln	Leu	Arg	Val	Phe	Val	Tyr	Arg	Thr	Ala	

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	455	460	465
5	Val Cys Ile Glu Asn Ser Cys Met Glu	Lys Gly Ser Lys Gln Gly	
	470	475	480
	Arg Asn Gly Ala Ile His Ile Phe Arg	Glu Ile Ile Lys Pro Ala	
	485	490	495
10	Glu Lys Ser Leu His Glu Lys Leu Lys	Gln Asp Lys Arg Phe Ser	
	500	505	510
	Thr Phe Leu Ser Leu Leu Glu Ala Ala	Asp Leu Lys Glu Leu Leu	
	515	520	525
15	Thr Gln Pro Gly Asp Trp Thr Leu Phe	Val Pro Thr Asn Asp Ala	
	530	535	540
	Phe Lys Gly Met Thr Ser Glu Glu Lys	Glu Ile Leu Ile Arg Asp	
	545	550	555
20	Lys Asn Ala Leu Gln Asn Ile Ile Leu	Tyr His Leu Thr Pro Gly	
	560	565	570
	Val Phe Ile Gly Lys Gly Phe Glu Pro	Gly Val Thr Asn Ile Leu	
	575	580	585
25	Lys Thr Thr Gln Gly Ser Lys Ile Phe	Leu Lys Glu Val Asn Asp	
	590	595	600
	Thr Leu Leu Val Asn Glu Leu Lys Ser	Lys Glu Ser Asp Ile Met	
	605	610	615
30	Thr Thr Asn Gly Val Ile His Val Val	Asp Lys Leu Leu Tyr Pro	
	620	625	630
	Ala Asp Thr Pro Val Gly Asn Asp Gln	Leu Leu Glu Ile Leu Asn	
	635	640	645
35	Lys Leu Ile Lys Tyr Ile Gln Ile Lys	Phe Val Arg Gly Ser Thr	
	650	655	660
	Phe Lys Glu Ile Pro Val Thr Val Tyr	Lys Pro Ile Ile Lys Lys	
	665	670	675
40	Tyr Thr Lys Ile Ile Asp Gly Val Pro	Val Glu Ile Thr Glu Lys	
	680	685	690
	Glu Thr Arg Glu Glu Arg Ile Ile Thr	Gly Pro Glu Ile Lys Tyr	
	695	700	705
45	Thr Arg Ile Ser Thr Gly Gly Gly Glu	Thr Glu Glu Thr Leu Lys	
	710	715	720
	Lys Leu Leu Gln Glu Asp Thr Pro Val	Arg Lys Leu Gln Ala Asn	
	725	730	735
50	Lys Lys Val Gln Gly Ser Arg Arg Arg	Leu Arg Glu Gly Arg Ser	
	740	745	750
55	Gln		

5 <210> 122
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10 <400> 122
 Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile
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 Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala
 20 25 30
 His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala
 15 35 40 45
 Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys
 50 55 60
 Lys Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val
 20 65 70 75
 Leu Tyr Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys
 80 85 90
 Gly Cys Pro Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu
 25 95 100 105
 Gly Ile Val Gly Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser
 110 115 120
 Lys Leu Arg Glu Glu Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe
 30 125 130 135
 Ala Pro Ser Asn Glu Ala Trp Asp Asn Leu Asp Ser Asp Ile Arg
 140 145 150
 Arg Gly Leu Glu Ser Asn Val Asn Val Glu Leu Leu Asn Ala Leu
 35 155 160 165
 His Ser His Met Ile Asn Lys Arg Met Leu Thr Lys Asp Leu Lys
 170 175 180
 Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu Gly Leu Phe
 40 185 190 195
 Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys Ala Arg
 200 205 210
 Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His Val
 45 215 220 225
 Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
 230 235 240
 Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile
 50 245 250 255
 Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr
 55 260 265 270

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	Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly	275	280	285
5	Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu	290	295	300
	Met Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile	305	310	315
10	Met Gly Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu	320	325	330
	Ile Gly Cys Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met	335	340	345
15	Val Asn Lys Lys Asp Ile Val Thr Asn Asn Gly Val Ile His Leu	350	355	360
	Ile Asp Gln Val Leu Ile Pro Asp Ser Ala Lys Gln Val Ile Glu	365	370	375
20	Leu Ala Gly Lys Gln Gln Thr Thr Phe Thr Asp Leu Val Ala Gln	380	385	390
	Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp Gly Glu Tyr Thr Leu	395	400	405
25	Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp Thr Leu Ser Met	410	415	420
	Asp Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His Ile Leu Lys	425	430	435
30	Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile Leu Glu	440	445	450
	Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr Ala	455	460	465
35	Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly	470	475	480
	Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala	485	490	495
40	Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser	500	505	510
	Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu	515	520	525
45	Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala	530	535	540
50	Phe Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp	545	550	555
	Lys Asn Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly	560	565	570
55	Val Phe Ile Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu			

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	575	580	585
5	Lys Thr Thr Gln Gly Ser Lys Ile Phe	Leu Lys Glu Val Asn Asp	
	590	595	600
	Thr Leu Leu Val Asn Glu Leu Lys Ser	Lys Glu Ser Asp Ile Met	
	605	610	615
10	Thr Thr Asn Gly Val Ile His Val Val	Asp Lys Leu Leu Tyr Pro	
	620	625	630
	Ala Asp Thr Pro Val Gly Asn Asp Gln	Leu Leu Glu Ile Leu Asn	
	635	640	645
15	Lys Leu Ile Lys Tyr Ile Gln Ile Lys	Phe Val Arg Gly Ser Thr	
	650	655	660
	Phe Lys Glu Ile Pro Val Thr Val Tyr	Arg Pro Thr Leu Thr Lys	
	665	670	675
20	Val Lys Ile Glu Gly Glu Pro Glu Phe	Arg Leu Ile Lys Glu Gly	
	680	685	690
	Glu Thr Ile Thr Glu Val Ile His Gly	Glu Pro Ile Ile Lys Lys	
	695	700	705
25	Tyr Thr Lys Ile Ile Asp Gly Val Pro	Val Glu Ile Thr Glu Lys	
	710	715	720
	Glu Thr Arg Glu Glu Arg Ile Ile Thr	Gly Pro Glu Ile Lys Tyr	
	725	730	735
30	Thr Arg Ile Ser Thr Gly Gly Gly Glu	Thr Glu Glu Thr Leu Lys	
	740	745	750
	Lys Leu Leu Gln Glu Asp Thr Pro Val	Arg Lys Leu Gln Ala Asn	
	755	760	765
35	Lys Lys Val Gln Gly Ser Arg Arg Arg	Leu Arg Glu Gly Arg Ser	
	770	775	780
	Gln		
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	<400> 123		
	Met Ile Pro Phe Leu Pro Met Phe Ser	Leu Leu Leu Leu Ile	
	1	5	10
	Val Asn Pro Ile Asn Ala Asn Asn His	Tyr Asp Lys Ile Leu Ala	
50	20	25	30
	His Ser Arg Ile Arg Gly Arg Asp Gln	Gly Pro Asn Val Cys Ala	
	35	40	45
55	Leu Gln Gln Ile Leu Gly Thr Lys Lys	Lys Tyr Phe Ser Thr Cys	
	50	55	60

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5	Lys Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val	65	70	75
	Leu Tyr Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys	80	85	90
10	Gly Cys Pro Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu	95	100	105
	Gly Ile Val Gly Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser	110	115	120
15	Lys Leu Arg Glu Glu Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe	125	130	135
	Ala Pro Ser Asn Glu Ala Trp Asp Asn Leu Asp Ser Asp Ile Arg	140	145	150
20	Arg Gly Leu Glu Ser Asn Val Asn Val Glu Leu Leu Asn Ala Leu	155	160	165
	His Ser His Met Ile Asn Lys Arg Met Leu Thr Lys Asp Leu Lys	170	175	180
25	Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu Gly Leu Phe	185	190	195
	Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys Ala Arg	200	205	210
30	Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His Val	215	220	225
	Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe	230	235	240
35	Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile	245	250	255
	Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr	260	265	270
40	Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly	275	280	285
	Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu	290	295	300
45	Met Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile	305	310	315
	Met Gly Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu	320	325	330
50	Ile Gly Cys Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met	335	340	345
	Val Asn Lys Lys Asp Ile Val Thr Asn Asn Gly Val Ile His Leu	350	355	360
55				

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	Ile Asp Gln Val	Leu Ile Pro Asp Ser	Ala Lys Gln Val	Ile Glu
		365	370	375
5	Leu Ala Gly Lys	Gln Gln Thr Thr Phe	Thr Asp Leu Val	Ala Gln
		380	385	390
	Leu Gly Leu Ala	Ser Ala Leu Arg Pro	Asp Gly Glu Tyr Thr	Leu
		395	400	405
10	Leu Ala Pro Val	Asn Asn Ala Phe Ser	Asp Asp Thr Leu Ser	Met
		410	415	420
	Asp Gln Arg Leu	Leu Lys Leu Ile Leu	Gln Asn His Ile Leu	Lys
		425	430	435
15	Val Lys Val Gly	Leu Asn Glu Leu Tyr	Asn Gly Gln Ile Leu	Glu
		440	445	450
	Thr Ile Gly Gly	Lys Gln Leu Arg Val	Phe Val Tyr Arg Thr	Ala
		455	460	465
20	Val Cys Ile Glu	Asn Ser Cys Met Glu	Lys Gly Ser Lys Gln	Gly
		470	475	480
	Arg Asn Gly Ala	Ile His Ile Phe Arg	Glu Ile Ile Lys Pro	Ala
		485	490	495
25	Glu Lys Ser Leu	His Glu Lys Leu Lys	Gln Asp Lys Arg Phe	Ser
		500	505	510
	Thr Phe Leu Ser	Leu Leu Glu Ala Ala	Asp Leu Lys Glu Leu	Leu
		515	520	525
	Thr Gln Pro Gly	Asp Trp Thr Leu Phe	Val Pro Thr Asn Asp	Ala
		530	535	540
	Phe Lys Gly Met	Thr Ser Glu Glu Lys	Glu Ile Leu Ile Arg	Asp
		545	550	555
35	Lys Asn Ala Leu	Gln Asn Ile Ile Leu	Tyr His Leu Thr Pro	Gly
		560	565	570
	Val Phe Ile Gly	Lys Gly Phe Glu Pro	Gly Val Thr Asn Ile	Leu
		575	580	585
	Lys Thr Thr Gln	Gly Ser Lys Ile Phe	Leu Lys Glu Val Asn	Asp
		590	595	600
45	Thr Leu Leu Val	Asn Glu Leu Lys Ser	Lys Glu Ser Asp Ile	Met
		605	610	615
	Thr Thr Asn Gly	Val Ile His Val Val	Asp Lys Leu Leu Tyr	Pro
		620	625	630
50	Ala Asp Thr Pro	Val Gly Asn Asp Gln	Leu Leu Glu Ile Leu	Asn
		635	640	645
	Lys Leu Ile Lys	Tyr Ile Gln Ile Lys	Phe Val Arg Gly Ser	Thr
		650	655	660
55	Phe Lys Glu Ile	Pro Val Thr Val Tyr	Lys Pro Ile Ile Lys	Lys

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		665		670		675
5	Tyr Thr Lys Ile	Ile Asp Gly Val Pro	Val Glu Ile Thr Glu Lys			
		680		685		690
	Glu Thr Arg Glu	Glu Arg Ile Ile Thr	Gly Pro Glu Ile Lys Tyr			
		695		700		705
10	Thr Arg Ile Ser	Thr Gly Gly Gly Glu	Thr Glu Glu Thr Leu Lys			
		710		715		720
	Lys Leu Leu Gln	Glu Glu Val Thr Lys	Val Thr Lys Phe Ile Glu			
		725		730		735
15	Gly Gly Asp Gly	His Leu Phe Glu Asp	Glu Glu Ile Lys Arg Leu			
		740		745		750
	Leu Gln Gly Asp	Thr Pro Val Arg Lys	Leu Gln Ala Asn Lys Lys			
		755		760		765
20	Val Gln Gly Ser	Arg Arg Arg Leu Arg	Glu Gly Arg Ser Gln			
		770		775		
	<210> 124					
	<211> 283					
25	<212> PRT					
	<213> Homo Sapien					
	<400> 124					
	Met Val Asn Tyr	Ala Trp Ala Gly Arg	Ser Gln Arg Lys Leu Trp			
	1	5	10			15
30	Trp Arg Ser Val	Ala Val Leu Thr Cys	Lys Ser Val Val Arg Pro			
		20	25			30
	Gly Tyr Arg Gly	Gly Leu Gln Ala Arg	Arg Ser Thr Leu Leu Lys			
		35	40			45
35	Thr Cys Ala Arg	Ala Arg Ala Thr Ala	Pro Gly Ala Met Lys Met			
		50	55			60
	Val Ala Pro Trp	Thr Arg Phe Tyr Ser	Asn Ser Cys Cys Leu Cys			
40		65	70			75
	Cys His Val Arg	Thr Gly Thr Ile Leu	Leu Gly Val Trp Tyr Leu			
		80	85			90
	Ile Ile Asn Ala	Val Val Leu Leu Ile	Leu Leu Ser Ala Leu Ala			
45		95	100			105
	Asp Pro Asp Gln	Tyr Asn Phe Ser Ser	Ser Glu Leu Gly Gly Asp			
		110	115			120
	Phe Glu Phe Met	Asp Asp Ala Asn Met	Cys Ile Ala Ile Ala Ile			
50		125	130			135
	Ser Leu Leu Met	Ile Leu Ile Cys Ala	Met Ala Thr Tyr Gly Ala			
		140	145			150
55	Tyr Lys Gln Arg	Ala Ala Trp Ile Ile	Pro Phe Phe Cys Tyr Gln			
		155	160			165

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5	Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala Ile Thr Val Leu	170	175	180
	Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln Leu Pro Pro	185	190	195
10	Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro Thr Cys	200	205	210
	Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr Phe	215	220	225
15	Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile	230	235	240
	Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser Asn	245	250	255
20	Asp Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn	260	265	270
	Gly Ala Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala	275	280	
25	<210> 125			
	<211> 254			
	<212> PRT			
	<213> Homo Sapien			
30	<400> 125			
	Met Pro Gly Gln Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu	1	5	10
	Lys Thr Cys Ala Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys	20	25	30
35	Met Val Ala Pro Trp Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu	35	40	45
	Cys Cys His Val Arg Thr Gly Thr Ile Leu Leu Gly Val Trp Tyr	50	55	60
40	Leu Ile Ile Asn Ala Val Val Leu Leu Ile Leu Leu Ser Ala Leu	65	70	75
	Ala Asp Pro Asp Gln Tyr Asn Phe Ser Ser Ser Glu Leu Gly Gly	80	85	90
45	Asp Phe Glu Phe Met Asp Asp Ala Asn Met Cys Ile Ala Ile Ala	95	100	105
	Ile Ser Leu Leu Met Ile Leu Ile Cys Ala Met Ala Thr Tyr Gly	110	115	120
50	Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro Phe Phe Cys Tyr	125	130	135
	Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala Ile Thr Val	140	145	150

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	Leu	Ile	Tyr	Pro	Asn	Ser	Ile	Gln	Glu	Tyr	Ile	Arg	Gln	Leu	Pro	
					155					160					165	
5	Pro	Asn	Phe	Pro	Tyr	Arg	Asp	Asp	Val	Met	Ser	Val	Asn	Pro	Thr	
					170					175					180	
	Cys	Leu	Val	Leu	Ile	Ile	Leu	Leu	Phe	Ile	Ser	Ile	Ile	Leu	Thr	
					185					190					195	
10	Phe	Lys	Gly	Tyr	Leu	Ile	Ser	Cys	Val	Trp	Asn	Cys	Tyr	Arg	Tyr	
					200					205					210	
	Ile	Asn	Gly	Arg	Asn	Ser	Ser	Asp	Val	Leu	Val	Tyr	Val	Thr	Ser	
					215					220					225	
15	Asn	Asp	Thr	Thr	Val	Leu	Leu	Pro	Pro	Tyr	Asp	Asp	Ala	Thr	Val	
					230					235					240	
	Asn	Gly	Ala	Ala	Lys	Glu	Pro	Pro	Pro	Pro	Tyr	Val	Ser	Ala		
					245					250						
20																
	<210> 126															
	<211> 539															
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	<213> Homo Sapien															
25																
	<400> 126															
	Met	Gly	Arg	Ala	Gly	Gly	Gly	Gly	Pro	Gly	Arg	Gly	Pro	Pro	Pro	
	1				5					10					15	
	Leu	Leu	Leu	Phe	Leu	Gly	Ala	Ala	Leu	Val	Leu	Ala	Ser	Gly	Ala	
30					20					25					30	
	Val	Pro	Ala	Arg	Glu	Ala	Gly	Ser	Ala	Val	Glu	Ala	Glu	Glu	Leu	
					35					40					45	
35	Val	Lys	Gly	Ser	Pro	Ala	Trp	Glu	Pro	Pro	Ala	Asn	Asp	Thr	Arg	
					50					55					60	
	Glu	Glu	Ala	Gly	Pro	Pro	Ala	Ala	Gly	Glu	Asp	Glu	Ala	Ser	Trp	
					65					70					75	
40	Thr	Ala	Pro	Gly	Gly	Glu	Leu	Ala	Gly	Pro	Glu	Glu	Val	Leu	Gln	
					80					85					90	
	Glu	Ser	Ala	Ala	Val	Thr	Gly	Thr	Ala	Trp	Leu	Glu	Ala	Asp	Ser	
					95					100					105	
45	Pro	Gly	Leu	Gly	Gly	Val	Thr	Ala	Glu	Ala	Gly	Ser	Gly	Asp	Ala	
					110					115					120	
	Gln	Ala	Leu	Pro	Ala	Thr	Leu	Gln	Ala	Pro	His	Glu	Val	Leu	Gly	
					125					130					135	
50	Gln	Ser	Ile	Met	Pro	Pro	Ala	Ile	Pro	Glu	Ala	Thr	Glu	Ala	Ser	
					140					145					150	
	Gly	Pro	Pro	Ser	Pro	Thr	Pro	Gly	Asp	Lys	Leu	Ser	Pro	Ala	Ser	
					155					160					165	
55	Glu	Leu	Pro	Lys	Glu	Ser	Pro	Leu	Glu	Val	Trp	Leu	Asn	Leu	Gly	

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					170					175					180	
5		Gly	Ser	Thr	Pro	Asp 185	Pro	Gln	Val	Pro	Glu 190	Leu	Thr	Tyr	Pro	Phe 195
		Gln	Gly	Thr	Leu	Glu 200	Pro	Gln	Pro	Ala	Ser 205	Asp	Ile	Ile	Asp	Ile 210
10		Asp	Tyr	Phe	Glu	Gly 215	Leu	Asp	Gly	Glu	Gly 220	Arg	Gly	Ala	Asp	Leu 225
		Gly	Ser	Phe	Pro	Gly 230	Ser	Pro	Gly	Thr	Ser 235	Glu	Asn	His	Pro	Asp 240
15		Thr	Glu	Gly	Glu	Thr 245	Pro	Ser	Trp	Ser	Leu 250	Leu	Asp	Leu	Tyr	Asp 255
		Asp	Phe	Thr	Pro	Phe 260	Asp	Glu	Ser	Asp	Phe 265	Tyr	Pro	Thr	Thr	Ser 270
20		Phe	Tyr	Asp	Asp	Leu 275	Asp	Glu	Glu	Glu	Glu 280	Glu	Glu	Glu	Asp	Asp 285
		Lys	Asp	Ala	Val	Gly 290	Gly	Gly	Asp	Leu	Glu 295	Asp	Glu	Asn	Glu	Leu 300
25		Leu	Val	Pro	Thr	Gly 305	Lys	Pro	Gly	Leu	Gly 310	Pro	Gly	Thr	Gly	Gln 315
		Pro	Thr	Ser	Arg	Trp 320	His	Ala	Val	Pro	Pro 325	Gln	His	Thr	Leu	Gly 330
30		Ser	Val	Pro	Gly	Ser 335	Ser	Ile	Ala	Leu	Arg 340	Pro	Arg	Pro	Gly	Glu 345
		Pro	Gly	Arg	Asp	Leu 350	Ala	Ser	Ser	Glu	Asn 355	Gly	Thr	Glu	Cys	Arg 360
35		Ser	Gly	Phe	Val	Arg 365	His	Asn	Gly	Ser	Cys 370	Arg	Ser	Val	Cys	Asp 375
		Leu	Phe	Pro	Ser	Tyr 380	Cys	His	Asn	Gly	Gly 385	Gln	Cys	Tyr	Leu	Val 390
40		Glu	Asn	Ile	Gly	Ala 395	Phe	Cys	Arg	Cys	Asn 400	Thr	Gln	Asp	Tyr	Ile 405
		Trp	His	Lys	Gly	Met 410	Arg	Cys	Glu	Ser	Ile 415	Ile	Thr	Asp	Phe	Gln 420
45		Val	Met	Cys	Val	Ala 425	Val	Gly	Ser	Ala	Ala 430	Leu	Val	Leu	Leu	Leu 435
		Leu	Phe	Met	Met	Thr 440	Val	Phe	Phe	Ala	Lys 445	Lys	Leu	Tyr	Leu	Leu 450
50		Lys	Thr	Glu	Asn	Thr 455	Lys	Leu	Arg	Arg	Thr 460	Asn	Lys	Phe	Arg	Thr 465
55		Pro	Ser	Glu	Leu	His 470	Asn	Asp	Asn	Phe	Ser 475	Leu	Ser	Thr	Ile	Ala 480

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5	Glu Gly Ser His Pro Asn Asp Asp Pro Ser Ala Pro His Lys Ile	485	490	495
	Gln Glu Val Leu Lys Ser Cys Leu Lys Glu Glu Glu Ser Phe Asn	500	505	510
10	Ile Gln Asn Ser Met Ser Pro Lys Leu Glu Gly Gly Lys Gly Asp	515	520	525
	Gln Ala Asp Leu Asp Val Asn Cys Leu Gln Asn Asn Leu Thr	530	535	
15	<210> 127			
	<211> 1325			
	<212> PRT			
	<213> Homo Sapien			
20	<400> 127			
	Met Leu Pro Val Tyr Gln Glu Val Lys Pro Asn Pro Leu Gln Asp	1	5	10 15
	Ala Asn Ile Cys Ser Arg Val Phe Phe Trp Trp Leu Asn Pro Leu	20	25	30
25	Phe Lys Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr	35	40	45
	Ser Val Leu Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu Leu	50	55	60
30	Gln Gly Phe Trp Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala	65	70	75
	Gln Lys Pro Ser Leu Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys	80	85	90
35	Ser Tyr Leu Val Leu Gly Ile Phe Thr Leu Ile Glu Glu Ser Ala	95	100	105
	Lys Val Ile Gln Pro Ile Phe Leu Gly Lys Ile Ile Asn Tyr Phe	110	115	120
40	Glu Asn Tyr Asp Pro Met Asp Ser Val Ala Leu Asn Thr Ala Tyr	125	130	135
	Ala Tyr Ala Thr Val Leu Thr Phe Cys Thr Leu Ile Leu Ala Ile	140	145	150
45	Leu His His Leu Tyr Phe Tyr His Val Gln Cys Ala Gly Met Arg	155	160	165
	Leu Arg Val Ala Met Cys His Met Ile Tyr Arg Lys Ala Leu Arg	170	175	180
50	Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly Gln Ile Val	185	190	195
55	Asn Leu Leu Ser Asn Asp Val Asn Lys Phe Asp Gln Val Thr Val	200	205	210

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	Phe	Leu	His	Phe	Leu	Trp	Ala	Gly	Pro	Leu	Gln	Ala	Ile	Ala	Val	215	220	225
5	Thr	Ala	Leu	Leu	Trp	Met	Glu	Ile	Gly	Ile	Ser	Cys	Leu	Ala	Gly	230	235	240
	Met	Ala	Val	Leu	Ile	Ile	Leu	Leu	Pro	Leu	Gln	Ser	Cys	Phe	Gly	245	250	255
10	Lys	Leu	Phe	Ser	Ser	Leu	Arg	Ser	Lys	Thr	Ala	Thr	Phe	Thr	Asp	260	265	270
	Ala	Arg	Ile	Arg	Thr	Met	Asn	Glu	Val	Ile	Thr	Gly	Ile	Arg	Ile	275	280	285
15	Ile	Lys	Met	Tyr	Ala	Trp	Glu	Lys	Ser	Phe	Ser	Asn	Leu	Ile	Thr	290	295	300
	Asn	Leu	Arg	Lys	Lys	Glu	Ile	Ser	Lys	Ile	Leu	Arg	Ser	Ser	Cys	305	310	315
20	Leu	Arg	Gly	Met	Asn	Leu	Ala	Ser	Phe	Phe	Ser	Ala	Ser	Lys	Ile	320	325	330
	Ile	Val	Phe	Val	Thr	Phe	Thr	Thr	Tyr	Val	Leu	Leu	Gly	Ser	Val	335	340	345
25	Ile	Thr	Ala	Ser	Arg	Val	Phe	Val	Ala	Val	Thr	Leu	Tyr	Gly	Ala	350	355	360
	Val	Arg	Leu	Thr	Val	Thr	Leu	Phe	Phe	Pro	Ser	Ala	Ile	Glu	Arg	365	370	375
30	Val	Ser	Glu	Ala	Ile	Val	Ser	Ile	Arg	Arg	Ile	Gln	Thr	Phe	Leu	380	385	390
	Leu	Leu	Asp	Glu	Ile	Ser	Gln	Arg	Asn	Arg	Gln	Leu	Pro	Ser	Asp	395	400	405
35	Gly	Lys	Lys	Met	Val	His	Val	Gln	Asp	Phe	Thr	Ala	Phe	Trp	Asp	410	415	420
40	Lys	Ala	Ser	Glu	Thr	Pro	Thr	Leu	Gln	Gly	Leu	Ser	Phe	Thr	Val	425	430	435
	Arg	Pro	Gly	Glu	Leu	Leu	Ala	Val	Val	Gly	Pro	Val	Gly	Ala	Gly	440	445	450
45	Lys	Ser	Ser	Leu	Leu	Ser	Ala	Val	Leu	Gly	Glu	Leu	Ala	Pro	Ser	455	460	465
	His	Gly	Leu	Val	Ser	Val	His	Gly	Arg	Ile	Ala	Tyr	Val	Ser	Gln	470	475	480
50	Gln	Pro	Trp	Val	Phe	Ser	Gly	Thr	Leu	Arg	Ser	Asn	Ile	Leu	Phe	485	490	495
	Gly	Lys	Lys	Tyr	Glu	Lys	Glu	Arg	Tyr	Glu	Lys	Val	Ile	Lys	Ala	500	505	510
55	Cys	Ala	Leu	Lys	Lys	Asp	Leu	Gln	Leu	Leu	Glu	Asp	Gly	Asp	Leu			

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					515					520					525
5	Thr	Val	Ile	Gly	Asp 530	Arg	Gly	Thr	Thr	Leu 535	Ser	Gly	Gly	Gln	Lys 540
	Ala	Arg	Val	Asn	Leu 545	Ala	Arg	Ala	Val	Tyr 550	Gln	Asp	Ala	Asp	Ile 555
10	Tyr	Leu	Leu	Asp	Asp 560	Pro	Leu	Ser	Ala	Val 565	Asp	Ala	Glu	Val	Ser 570
	Arg	His	Leu	Phe	Glu 575	Leu	Cys	Ile	Cys	Gln 580	Ile	Leu	His	Glu	Lys 585
15	Ile	Thr	Ile	Leu	Val 590	Thr	His	Gln	Leu	Gln 595	Tyr	Leu	Lys	Ala	Ala 600
	Ser	Gln	Ile	Leu	Ile 605	Leu	Lys	Asp	Gly	Lys 610	Met	Val	Gln	Lys	Gly 615
20	Thr	Tyr	Thr	Glu	Phe 620	Leu	Lys	Ser	Gly	Ile 625	Asp	Phe	Gly	Ser	Leu 630
	Leu	Lys	Lys	Asp	Asn 635	Glu	Glu	Ser	Glu	Gln 640	Pro	Pro	Val	Pro	Gly 645
25	Thr	Pro	Thr	Leu	Arg 650	Asn	Arg	Thr	Phe	Ser 655	Glu	Ser	Ser	Val	Trp 660
	Ser	Gln	Gln	Ser	Ser 665	Arg	Pro	Ser	Leu	Lys 670	Asp	Gly	Ala	Leu	Glu 675
30	Ser	Gln	Asp	Thr	Glu 680	Asn	Val	Pro	Val	Thr 685	Leu	Ser	Glu	Glu	Asn 690
	Arg	Ser	Glu	Gly	Lys 695	Val	Gly	Phe	Gln	Ala 700	Tyr	Lys	Asn	Tyr	Phe 705
35	Arg	Ala	Gly	Ala	His 710	Trp	Ile	Val	Phe	Ile 715	Phe	Leu	Ile	Leu	Leu 720
	Asn	Thr	Ala	Ala	Gln 725	Val	Ala	Tyr	Val	Leu 730	Gln	Asp	Trp	Trp	Leu 735
40	Ser	Tyr	Trp	Ala	Asn 740	Lys	Gln	Ser	Met	Leu 745	Asn	Val	Thr	Val	Asn 750
	Gly	Gly	Gly	Asn	Val 755	Thr	Glu	Lys	Leu	Asp 760	Leu	Asn	Trp	Tyr	Leu 765
45	Gly	Ile	Tyr	Ser	Gly 770	Leu	Thr	Val	Ala	Thr 775	Val	Leu	Phe	Gly	Ile 780
	Ala	Arg	Ser	Leu	Leu 785	Val	Phe	Tyr	Val	Leu 790	Val	Asn	Ser	Ser	Gln 795
50	Thr	Leu	His	Asn	Lys 800	Met	Phe	Glu	Ser	Ile 805	Leu	Lys	Ala	Pro	Val 810
	Leu	Phe	Phe	Asp	Arg 815	Asn	Pro	Ile	Gly	Arg 820	Ile	Leu	Asn	Arg	Phe 825
55															

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5	Ser Lys Asp Ile Gly His Leu Asp Asp Leu Leu Pro Leu Thr Phe	830	835	840
	Leu Asp Phe Ile Gln Thr Leu Leu Gln Val Val Gly Val Val Ser	845	850	855
10	Val Ala Val Ala Val Ile Pro Trp Ile Ala Ile Pro Leu Val Pro	860	865	870
	Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg Tyr Phe Leu Glu Thr	875	880	885
15	Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr Arg Ser Pro Val	890	895	900
	Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp Thr Ile Arg	905	910	915
20	Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp Ala His	920	925	930
	Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr Ser	935	940	945
25	Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val	950	955	960
	Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp	965	970	975
30	Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met	980	985	990
	Gly Met Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn	995	1000	1005
35	Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu	1010	1015	1020
	Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp	1025	1030	1035
40	Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr	1040	1045	1050
	Ser Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile	1055	1060	1065
45	Lys Ser Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly	1070	1075	1080
	Lys Ser Ser Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu	1085	1090	1095
50	Gly Lys Ile Trp Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu	1100	1105	1110
55	His Asp Leu Arg Lys Lys Met Ser Ile Ile Pro Gln Glu Pro Val	1115	1120	1125

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Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp Pro Phe Lys Glu
 1130 1135 1140
 5 His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu Val Gln Leu
 1145 1150 1155
 Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr Glu Leu
 1160 1165 1170
 10 Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu Val
 1175 1180 1185
 Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
 1190 1195 1200
 15 Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr Asp Glu Leu Ile
 1205 1210 1215
 Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr
 1220 1225 1230
 20 Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met
 1235 1240 1245
 Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val
 1250 1255 1260
 25 Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln
 1265 1270 1275
 Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln
 1280 1285 1290
 30 Val Tyr Phe Lys Arg Asn Tyr Pro His Ile Gly His Thr Asp His
 1295 1300 1305
 Met Val Thr Asn Thr Ser Asn Gly Gln Pro Ser Thr Leu Thr Ile
 1310 1315 1320
 35 Phe Glu Thr Ala Leu
 1325
 40 <210> 128
 <211> 501
 <212> PRT
 <213> Homo Sapien
 <400> 128
 45 Met Ser Ala Leu Arg Arg Lys Phe Gly Asp Asp Tyr Gln Val Val
 1 5 10 15
 Thr Thr Ser Ser Ser Gly Ser Gly Leu Gln Pro Gln Gly Pro Gly
 20 25 30
 50 Gln Asp Pro Gln Gln Gln Leu Val Pro Lys Lys Lys Arg Gln Arg
 35 40 45
 Phe Val Asp Lys Asn Gly Arg Cys Asn Val Gln His Gly Asn Leu
 50 55 60
 55 Gly Ser Glu Thr Ser Arg Tyr Leu Ser Asp Leu Phe Thr Thr Leu

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					65					70					75
5	Val	Asp	Leu	Lys	Trp	Arg	Trp	Asn	Leu	Phe	Ile	Phe	Ile	Leu	Thr
					80					85					90
	Tyr	Thr	Val	Ala	Trp	Leu	Phe	Met	Ala	Ser	Met	Trp	Trp	Val	Ile
					95					100					105
10	Ala	Tyr	Thr	Arg	Gly	Asp	Leu	Asn	Lys	Ala	His	Val	Gly	Asn	Tyr
					110					115					120
	Thr	Pro	Cys	Val	Ala	Asn	Val	Tyr	Asn	Phe	Pro	Ser	Ala	Phe	Leu
					125					130					135
15	Phe	Phe	Ile	Glu	Thr	Glu	Ala	Thr	Ile	Gly	Tyr	Gly	Tyr	Arg	Tyr
					140					145					150
	Ile	Thr	Asp	Lys	Cys	Pro	Glu	Gly	Ile	Ile	Leu	Phe	Leu	Phe	Gln
					155					160					165
20	Ser	Ile	Leu	Gly	Ser	Ile	Val	Asp	Ala	Phe	Leu	Ile	Gly	Cys	Met
					170					175					180
	Phe	Ile	Lys	Met	Ser	Gln	Pro	Lys	Lys	Arg	Ala	Glu	Thr	Leu	Met
					185					190					195
25	Phe	Ser	Glu	His	Ala	Val	Ile	Ser	Met	Arg	Asp	Gly	Lys	Leu	Thr
					200					205					210
	Leu	Met	Phe	Arg	Val	Gly	Asn	Leu	Arg	Asn	Ser	His	Met	Val	Ser
					215					220					225
30	Ala	Gln	Ile	Arg	Cys	Lys	Leu	Leu	Lys	Ser	Arg	Gln	Thr	Pro	Glu
					230					235					240
	Gly	Glu	Phe	Leu	Pro	Leu	Asp	Gln	Leu	Glu	Leu	Asp	Val	Gly	Phe
					245					250					255
35	Ser	Thr	Gly	Ala	Asp	Gln	Leu	Phe	Leu	Val	Ser	Pro	Leu	Thr	Ile
					260					265					270
	Cys	His	Val	Ile	Asp	Ala	Lys	Ser	Pro	Phe	Tyr	Asp	Leu	Ser	Gln
					275					280					285
40	Arg	Ser	Met	Gln	Thr	Glu	Gln	Phe	Glu	Ile	Val	Val	Ile	Leu	Glu
					290					295					300
	Gly	Ile	Val	Glu	Thr	Thr	Gly	Met	Thr	Cys	Gln	Ala	Arg	Thr	Ser
					305					310					315
45	Tyr	Thr	Glu	Asp	Glu	Val	Leu	Trp	Gly	His	Arg	Phe	Phe	Pro	Val
					320					325					330
	Ile	Ser	Leu	Glu	Glu	Gly	Phe	Phe	Lys	Val	Asp	Tyr	Ser	Gln	Phe
					335					340					345
50	His	Ala	Thr	Phe	Glu	Val	Pro	Thr	Pro	Pro	Tyr	Ser	Val	Lys	Glu
					350					355					360
55	Gln	Glu	Glu	Met	Leu	Leu	Met	Ser	Ser	Pro	Leu	Ile	Ala	Pro	Ala
					365					370					375

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5	Ile Thr Asn Ser Lys Glu Arg His Asn Ser Val Glu Cys Leu Asp	380	385	390
	Gly Leu Asp Asp Ile Thr Thr Lys Leu Pro Ser Lys Leu Gln Lys	395	400	405
10	Ile Thr Gly Arg Glu Asp Phe Pro Lys Lys Leu Leu Arg Met Ser	410	415	420
	Ser Thr Thr Ser Glu Lys Ala Tyr Ser Leu Gly Asp Leu Pro Met	425	430	435
15	Lys Leu Gln Arg Ile Ser Ser Val Pro Gly Asn Ser Glu Glu Lys	440	445	450
	Leu Val Ser Lys Thr Thr Lys Met Leu Ser Asp Pro Met Ser Gln	455	460	465
20	Ser Val Ala Asp Leu Pro Pro Lys Leu Gln Lys Met Ala Gly Gly	470	475	480
	Ala Ala Arg Met Glu Gly Asn Leu Pro Ala Lys Leu Arg Lys Met	485	490	495
25	Asn Ser Asp Arg Phe Thr	500		
30	<210> 129 <211> 1148 <212> PRT <213> Homo Sapien			
	<400> 129			
	Met Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly	1	5	10
35	Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr	20	25	30
	Arg Val Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro	35	40	45
40	Gly Leu Asp Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr	50	55	60
	His Gly Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser	65	70	75
45	Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Met Thr Thr Thr	80	85	90
	Arg Thr Pro Asp Thr Ser Thr Met His Leu Ala Thr Ser Arg Thr	95	100	105
50	Pro Ala Ser Leu Ser Gly Pro Thr Thr Ala Ser Pro Leu Leu Val	110	115	120
55	Leu Phe Thr Ile Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu	125	130	135

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	Asn Met His His	Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg	140	145	150
5	Val Leu Gln Gly	Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val	155	160	165
	Gly Pro Leu Tyr	Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys	170	175	180
10	Lys Asp Gly Ala	Ala Thr Lys Val Asp Ala Ile Cys Thr Tyr Arg	185	190	195
	Pro Asp Pro Lys	Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp	200	205	210
15	Glu Leu Ser Gln	Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr	215	220	225
	Thr Leu Asp Arg	Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg	230	235	240
20	Ser Ser Val Pro	Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp	245	250	255
	Leu Gly Thr Ser	Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala	260	265	270
25	Ala Ser Pro Leu	Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr	275	280	285
	Asn Leu Arg Tyr	Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys	290	295	300
30	Phe Asn Thr Thr	Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu	305	310	315
	Phe Lys Ser Thr	Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu	320	325	330
35	Thr Leu Leu Arg	Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp	335	340	345
	Ala Ile Cys Thr	His His Pro Asp Pro Lys Ser Pro Arg Leu Asp	350	355	360
40	Arg Glu Gln Leu	Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile	365	370	375
	Thr Glu Leu Gly	His Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val	380	385	390
45	Asn Gly Phe Thr	His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro	395	400	405
	Gly Thr Pro Thr	Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser	410	415	420
50	Ile Phe Gly Pro	Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr	425	430	435
55	Leu Asn Phe Thr	Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp			

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					440						445					450
5		Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu	Arg	Val	Leu	Gln	Gly
						455					460					465
		Leu	Leu	Arg	Pro	Leu	Phe	Lys	Asn	Thr	Ser	Val	Gly	Pro	Leu	Tyr
						470					475					480
10		Ser	Gly	Ser	Arg	Leu	Thr	Leu	Leu	Arg	Pro	Glu	Lys	Asp	Gly	Glu
						485					490					495
		Ala	Thr	Gly	Val	Asp	Ala	Ile	Cys	Thr	His	Arg	Pro	Asp	Pro	Thr
						500					505					510
15		Gly	Pro	Gly	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Leu	Glu	Leu	Ser	Gln
						515					520					525
		Leu	Thr	His	Ser	Ile	Thr	Glu	Leu	Gly	Pro	Tyr	Thr	Leu	Asp	Arg
						530					535					540
20		Asp	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr	His	Arg	Ser	Ser	Val	Pro
						545					550					555
		Thr	Thr	Ser	Thr	Gly	Val	Val	Ser	Glu	Glu	Pro	Phe	Thr	Leu	Asn
						560					565					570
25		Phe	Thr	Ile	Asn	Asn	Leu	Arg	Tyr	Met	Ala	Asp	Met	Gly	Gln	Pro
						575					580					585
		Gly	Ser	Leu	Lys	Phe	Asn	Ile	Thr	Asp	Asn	Val	Met	Lys	His	Leu
						590					595					600
30		Leu	Ser	Pro	Leu	Phe	Gln	Arg	Ser	Ser	Leu	Gly	Ala	Arg	Tyr	Thr
						605					610					615
		Gly	Cys	Arg	Val	Ile	Ala	Leu	Arg	Ser	Val	Lys	Asn	Gly	Ala	Glu
						620					625					630
35		Thr	Arg	Val	Asp	Leu	Leu	Cys	Thr	Tyr	Leu	Gln	Pro	Leu	Ser	Gly
						635					640					645
		Pro	Gly	Leu	Pro	Ile	Lys	Gln	Val	Phe	His	Glu	Leu	Ser	Gln	Gln
						650					655					660
40		Thr	His	Gly	Ile	Thr	Arg	Leu	Gly	Pro	Tyr	Ser	Leu	Asp	Lys	Asp
						665					670					675
		Ser	Leu	Tyr	Leu	Asn	Gly	Tyr	Asn	Glu	Pro	Gly	Leu	Asp	Glu	Pro
						680					685					690
45		Pro	Thr	Thr	Pro	Lys	Pro	Ala	Thr	Thr	Phe	Leu	Pro	Pro	Leu	Ser
						695					700					705
		Glu	Ala	Thr	Thr	Ala	Met	Gly	Tyr	His	Leu	Lys	Thr	Leu	Thr	Leu
						710					715					720
50		Asn	Phe	Thr	Ile	Ser	Asn	Leu	Gln	Tyr	Ser	Pro	Asp	Met	Gly	Lys
						725					730					735
55		Gly	Ser	Ala	Thr	Phe	Asn	Ser	Thr	Glu	Gly	Val	Leu	Gln	His	Leu
						740					745					750

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5	Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu	755	760	765
	Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala	770	775	780
10	Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly	785	790	795
	Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu	800	805	810
15	Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp	815	820	825
	Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg	830	835	840
20	Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser	845	850	855
	Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp	860	865	870
25	Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His	875	880	885
	Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser	890	895	900
30	Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro	905	910	915
	Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser	920	925	930
35	Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val	935	940	945
	Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser	950	955	960
40	Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr	965	970	975
	Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn	980	985	990
45	Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser	995	1000	1005
	Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg	1010	1015	1020
50	Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn	1025	1030	1035
	Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu	1040	1045	1050
55				

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	Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe	
	1055	1060 1065
5	Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn	
	1070	1075 1080
	Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala	
	1085	1090 1095
10	Val Ile Phe Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys	
	1100	1105 1110
	Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu	
	1115	1120 1125
15	Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser	
	1130	1135 1140
	His Leu Asp Leu Glu Asp Leu Gln	
	1145	
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	<212> PRT	
	<213> Homo Sapien	
25	<400> 130	
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	1 5 10 15	
	Val Val Trp Leu Gly Leu Asn Val Phe Leu Phe Val Asp Ala Phe	
30	20 25 30	
	Leu Lys Tyr Glu Lys Ala Asp Lys Tyr Tyr Tyr Thr Arg Lys Ile	
	35 40 45	
	Leu Gly Ser Thr Leu Ala Cys Ala Arg Ala Ser Ala Leu Cys Leu	
35	50 55 60	
	Asn Phe Asn Ser Thr Leu Ile Leu Leu Pro Val Cys Arg Asn Leu	
	65 70 75	
40	Leu Ser Phe Leu Arg Gly Thr Cys Ser Phe Cys Ser Arg Thr Leu	
	80 85 90	
	Arg Lys Gln Leu Asp His Asn Leu Thr Phe His Lys Leu Val Ala	
	95 100 105	
45	Tyr Met Ile Cys Leu His Thr Ala Ile His Ile Ile Ala His Leu	
	110 115 120	
	Phe Asn Phe Asp Cys Tyr Ser Arg Ser Arg Gln Ala Thr Asp Gly	
	125 130 135	
50	Ser Leu Ala Ser Ile Leu Ser Ser Leu Ser His Asp Glu Lys Lys	
	140 145 150	
	Gly Gly Ser Trp Leu Asn Pro Ile Gln Ser Arg Asn Thr Thr Val	
	155 160 165	
55	Glu Tyr Val Thr Phe Thr Ser Val Ala Gly Leu Thr Gly Val Ile	

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					170					175						180
5		Met	Thr	Ile	Ala	Leu	Ile	Leu	Met	Val	Thr	Ser	Ala	Thr	Glu	Phe
						185										195
		Ile	Arg	Arg	Ser	Tyr	Phe	Glu	Val	Phe	Trp	Tyr	Thr	His	His	Leu
						200										210
10		Phe	Ile	Phe	Tyr	Ile	Leu	Gly	Leu	Gly	Ile	His	Gly	Ile	Gly	Gly
						215										225
		Ile	Val	Arg	Gly	Gln	Thr	Glu	Glu	Ser	Met	Asn	Glu	Ser	His	Pro
						230										240
15		Arg	Lys	Cys	Ala	Glu	Ser	Phe	Glu	Met	Trp	Asp	Asp	Arg	Asp	Ser
						245										255
		His	Cys	Arg	Arg	Pro	Lys	Phe	Glu	Gly	His	Pro	Pro	Glu	Ser	Trp
						260										270
20		Lys	Trp	Ile	Leu	Ala	Pro	Val	Ile	Leu	Tyr	Ile	Cys	Glu	Arg	Ile
						275										285
		Leu	Arg	Phe	Tyr	Arg	Ser	Gln	Gln	Lys	Val	Val	Ile	Thr	Lys	Val
						290										300
25		Val	Met	His	Pro	Ser	Lys	Val	Leu	Glu	Leu	Gln	Met	Asn	Lys	Arg
						305										315
		Gly	Phe	Ser	Met	Glu	Val	Gly	Gln	Tyr	Ile	Phe	Val	Asn	Cys	Pro
						320										330
30		Ser	Ile	Ser	Leu	Leu	Glu	Trp	His	Pro	Phe	Thr	Leu	Thr	Ser	Ala
						335										345
		Pro	Glu	Glu	Asp	Phe	Phe	Ser	Ile	His	Ile	Arg	Ala	Ala	Gly	Asp
						350										360
35		Trp	Thr	Glu	Asn	Leu	Ile	Arg	Ala	Phe	Glu	Gln	Gln	Tyr	Ser	Pro
						365										375
		Ile	Pro	Arg	Ile	Glu	Val	Asp	Gly	Pro	Phe	Gly	Thr	Ala	Ser	Glu
						380										390
40		Asp	Val	Phe	Gln	Tyr	Glu	Val	Ala	Val	Leu	Val	Gly	Ala	Gly	Ile
						395										405
		Gly	Val	Thr	Pro	Phe	Ala	Ser	Ile	Leu	Lys	Ser	Ile	Trp	Tyr	Lys
						410										420
45		Phe	Gln	Cys	Ala	Asp	His	Asn	Leu	Lys	Thr	Lys	Lys	Ile	Tyr	Phe
						425										435
		Tyr	Trp	Ile	Cys	Arg	Glu	Thr	Gly	Ala	Phe	Ser	Trp	Phe	Asn	Asn
						440										450
50		Leu	Leu	Thr	Ser	Leu	Glu	Gln	Glu	Met	Glu	Glu	Leu	Gly	Lys	Val
						455										465
		Gly	Phe	Leu	Asn	Tyr	Arg	Leu	Phe	Leu	Thr	Gly	Trp	Asp	Ser	Asn
						470										480
55																

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5	Ile Val Gly His Ala Ala Leu Asn Phe Asp Lys Ala Thr Asp Ile	485	490	495
	Val Thr Gly Leu Lys Gln Lys Thr Ser Phe Gly Arg Pro Met Trp	500	505	510
10	Asp Asn Glu Phe Ser Thr Ile Ala Thr Ser His Pro Lys Ser Val	515	520	525
	Val Gly Val Phe Leu Cys Gly Pro Arg Thr Leu Ala Lys Ser Leu	530	535	540
15	Arg Lys Cys Cys His Arg Tyr Ser Ser Leu Asp Pro Arg Lys Val	545	550	555
	Gln Phe Tyr Phe Asn Lys Glu Asn Phe	560		
20	<210> 131			
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	<213> Homo Sapien			
25	<400> 131			
	Met Gly Asn Trp Val Val Asn His Trp Phe Ser Val Leu Phe Leu	1	5	10 15
	Val Val Trp Leu Gly Leu Asn Val Phe Leu Phe Val Asp Ala Phe	20	25	30
30	Leu Lys Tyr Glu Lys Ala Asp Lys Tyr Tyr Tyr Thr Arg Lys Ile	35	40	45
	Leu Gly Ser Thr Leu Ala Cys Ala Arg Ala Ser Ala Leu Cys Leu	50	55	60
35	Asn Phe Asn Ser Thr Leu Ile Leu Leu Pro Val Cys Arg Asn Leu	65	70	75
	Leu Ser Phe Leu Arg Gly Thr Cys Ser Phe Cys Ser Arg Thr Leu	80	85	90
40	Arg Lys Gln Leu Asp His Asn Leu Thr Phe His Lys Leu Val Ala	95	100	105
	Tyr Met Ile Cys Leu His Thr Ala Ile His Ile Ile Ala His Leu	110	115	120
45	Phe Asn Phe Asp Cys Tyr Ser Arg Ser Arg Gln Ala Thr Asp Gly	125	130	135
	Ser Leu Ala Ser Ile Leu Ser Ser Leu Ser His Asp Glu Lys Lys	140	145	150
50	Gly Gly Ser Trp Leu Asn Pro Ile Gln Ser Arg Asn Thr Thr Val	155	160	165
55	Glu Tyr Val Thr Phe Thr Ser Ile Ala Gly Leu Thr Gly Val Ile	170	175	180

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	Met Thr Ile Ala	Leu Ile Leu Met Val	Thr Ser Ala Thr Glu Phe
		185	190 195
5	Ile Arg Arg Ser	Tyr Phe Glu Val Phe	Trp Tyr Thr His His Leu
		200	205 210
	Phe Ile Phe Tyr	Ile Leu Gly Leu Gly	Ile His Gly Ile Gly Gly
		215	220 225
10	Ile Val Arg Gly	Gln Thr Glu Glu Ser	Met Asn Glu Ser His Pro
		230	235 240
	Arg Lys Cys Ala	Glu Ser Phe Glu Met	Trp Asp Asp Arg Asp Ser
		245	250 255
15	His Cys Arg Arg	Pro Lys Phe Glu Gly	His Pro Pro Glu Ser Trp
		260	265 270
	Lys Trp Ile Leu	Ala Pro Val Ile Leu	Tyr Ile Cys Glu Arg Ile
		275	280 285
20	Leu Arg Phe Tyr	Arg Ser Gln Gln Lys	Val Val Ile Thr Lys Val
		290	295 300
	Val Met His Pro	Ser Lys Val Leu Glu	Leu Gln Met Asn Lys Arg
		305	310 315
25	Gly Phe Ser Met	Glu Val Gly Gln Tyr	Ile Phe Val Asn Cys Pro
		320	325 330
	Ser Ile Ser Leu	Leu Glu Trp His Pro	Phe Thr Leu Thr Ser Ala
		335	340 345
30	Pro Glu Glu Asp	Phe Phe Ser Ile His	Ile Arg Ala Ala Gly Asp
		350	355 360
	Trp Thr Glu Asn	Leu Ile Arg Ala Phe	Glu Gln Gln Tyr Ser Pro
		365	370 375
35	Ile Pro Arg Ile	Glu Val Asp Gly Pro	Phe Gly Thr Ala Ser Glu
		380	385 390
	Asp Val Phe Gln	Tyr Glu Val Ala Val	Leu Val Gly Ala Gly Ile
		395	400 405
40	Gly Val Thr Pro	Phe Ala Ser Ile Leu	Lys Ser Ile Trp Tyr Lys
		410	415 420
45	Phe Gln Cys Ala	Asp His Asn Leu Lys	Thr Lys Lys Ile Tyr Phe
		425	430 435
	Tyr Trp Ile Cys	Arg Glu Thr Gly Ala	Phe Ser Trp Phe Asn Asn
		440	445 450
50	Leu Leu Thr Ser	Leu Glu Gln Glu Met	Glu Glu Leu Gly Lys Val
		455	460 465
	Gly Phe Leu Asn	Tyr Arg Leu Phe Leu	Thr Gly Trp Asp Ser Asn
		470	475 480
55	Ile Val Gly His	Ala Ala Leu Asn Phe	Asp Lys Ala Thr Asp Ile

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					485					490					495
5	Val	Thr	Gly	Leu	Lys	Gln	Lys	Thr	Ser	Phe	Gly	Arg	Pro	Met	Trp
					500					505					510
	Asp	Asn	Glu	Phe	Ser	Thr	Ile	Ala	Thr	Ser	His	Pro	Lys	Ser	Val
					515					520					525
10	Val	Gly	Val	Phe	Leu	Cys	Gly	Pro	Arg	Thr	Leu	Ala	Lys	Ser	Leu
					530					535					540
	Arg	Lys	Cys	Cys	His	Arg	Tyr	Ser	Ser	Leu	Asp	Pro	Arg	Lys	Val
					545					550					555
15	Gln	Phe	Tyr	Phe	Asn	Lys	Glu	Asn	Phe						
					560										
	<210> 132														
	<211> 294														
	<212> PRT														
20	<213> Homo Sapien														
	<400> 132														
	Met	Gly	Asn	Trp	Val	Val	Asn	His	Trp	Phe	Ser	Val	Leu	Phe	Leu
	1				5					10					15
25	Val	Val	Trp	Leu	Gly	Leu	Asn	Val	Phe	Leu	Phe	Val	Asp	Ala	Phe
					20					25					30
	Leu	Lys	Tyr	Glu	Lys	Ala	Asp	Lys	Tyr	Tyr	Tyr	Thr	Arg	Lys	Ile
					35					40					45
30	Leu	Gly	Ser	Trp	Lys	Trp	Ile	Leu	Ala	Pro	Val	Ile	Leu	Tyr	Ile
					50					55					60
	Cys	Glu	Arg	Ile	Leu	Arg	Phe	Tyr	Arg	Ser	Gln	Gln	Lys	Val	Val
					65					70					75
35	Ile	Thr	Lys	Val	Val	Met	His	Pro	Ser	Lys	Val	Leu	Glu	Leu	Gln
					80					85					90
	Met	Asn	Lys	Arg	Gly	Phe	Ser	Met	Glu	Val	Gly	Gln	Tyr	Ile	Phe
					95					100					105
40	Val	Asn	Cys	Pro	Ser	Ile	Ser	Leu	Leu	Glu	Trp	His	Pro	Phe	Thr
					110					115					120
	Leu	Thr	Ser	Ala	Pro	Glu	Glu	Asp	Phe	Phe	Ser	Ile	His	Ile	Arg
					125					130					135
45	Ala	Ala	Gly	Asp	Trp	Thr	Glu	Asn	Leu	Ile	Arg	Ala	Phe	Glu	Gln
					140					145					150
	Gln	Tyr	Ser	Pro	Ile	Pro	Arg	Ile	Glu	Val	Asp	Gly	Pro	Phe	Gly
					155					160					165
50	Thr	Ala	Ser	Glu	Asp	Val	Phe	Gln	Tyr	Glu	Val	Ala	Val	Leu	Val
					170					175					180
55	Gly	Ala	Gly	Ile	Gly	Val	Thr	Pro	Phe	Ala	Ser	Ile	Leu	Lys	Ser
					185					190					195

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5	Ile Trp Tyr Lys Phe Gln Cys Ala Asp His Asn Leu Lys Thr Lys	200	205	210
	Lys Val Gly His Ala Ala Leu Asn Phe Asp Lys Ala Thr Asp Ile	215	220	225
10	Val Thr Gly Leu Lys Gln Lys Thr Ser Phe Gly Arg Pro Met Trp	230	235	240
	Asp Asn Glu Phe Ser Thr Ile Ala Thr Ser His Pro Lys Ser Val	245	250	255
15	Val Gly Val Phe Leu Cys Gly Pro Arg Thr Leu Ala Lys Ser Leu	260	265	270
	Arg Lys Cys Cys His Arg Tyr Ser Ser Leu Asp Pro Arg Lys Val	275	280	285
20	Gln Phe Tyr Phe Asn Lys Glu Asn Phe	290		
25	<210> 133 <211> 515 <212> PRT <213> Homo Sapien			
	<400> 133			
	Met Gly Asn Trp Val Val Asn His Trp Phe Ser Val Leu Phe Leu	1	5	10 15
30	Val Val Trp Leu Gly Leu Asn Val Phe Leu Phe Val Asp Ala Phe	20	25	30
	Leu Lys Tyr Glu Lys Ala Asp Lys Tyr Tyr Tyr Thr Arg Lys Ile	35	40	45
35	Leu Gly Ser Thr Leu Ala Cys Ala Arg Ala Ser Ala Leu Cys Leu	50	55	60
	Asn Phe Asn Ser Thr Leu Ile Leu Leu Pro Val Cys Arg Asn Leu	65	70	75
40	Leu Ser Phe Leu Arg Gly Thr Cys Ser Phe Cys Ser Arg Thr Leu	80	85	90
	Arg Lys Gln Leu Asp His Asn Leu Thr Phe His Lys Leu Val Ala	95	100	105
45	Tyr Met Ile Cys Leu His Thr Ala Ile His Ile Ile Ala His Leu	110	115	120
	Phe Asn Phe Asp Cys Tyr Ser Arg Ser Arg Gln Ala Thr Asp Gly	125	130	135
50	Ser Leu Ala Ser Ile Leu Ser Ser Leu Ser His Asp Glu Lys Lys	140	145	150
55	Gly Gly Ser Trp Leu Asn Pro Ile Gln Ser Arg Asn Thr Thr Val	155	160	165

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	Glu Tyr Val Thr Phe Thr Ser Ile Ala Gly Leu Thr Gly Val Ile	170	175	180
5	Met Thr Ile Ala Leu Ile Leu Met Val Thr Ser Ala Thr Glu Phe	185	190	195
	Ile Arg Arg Ser Tyr Phe Glu Val Phe Trp Tyr Thr His His Leu	200	205	210
10	Phe Ile Phe Tyr Ile Leu Gly Leu Gly Ile His Gly Ile Gly Gly	215	220	225
	Ile Val Arg Gly Gln Thr Glu Glu Ser Met Asn Glu Ser His Pro	230	235	240
15	Arg Lys Cys Ala Glu Ser Phe Glu Met Trp Asp Asp Arg Asp Ser	245	250	255
	His Cys Arg Arg Pro Lys Phe Glu Gly His Pro Pro Glu Ser Trp	260	265	270
20	Lys Trp Ile Leu Ala Pro Val Ile Leu Tyr Ile Cys Glu Arg Ile	275	280	285
	Leu Arg Phe Tyr Arg Ser Gln Gln Lys Val Val Ile Thr Lys Val	290	295	300
25	Val Met His Pro Ser Lys Val Leu Glu Leu Gln Met Asn Lys Arg	305	310	315
	Gly Phe Ser Met Glu Val Gly Gln Tyr Ile Phe Val Asn Cys Pro	320	325	330
30	Ser Ile Ser Leu Leu Glu Trp His Pro Phe Thr Leu Thr Ser Ala	335	340	345
	Pro Glu Glu Asp Phe Phe Ser Ile His Ile Arg Ala Ala Gly Asp	350	355	360
35	Trp Thr Glu Asn Leu Ile Arg Ala Phe Glu Gln Gln Tyr Ser Pro	365	370	375
	Ile Pro Arg Ile Glu Val Asp Gly Pro Phe Gly Thr Ala Ser Glu	380	385	390
40	Asp Val Phe Gln Tyr Glu Val Ala Val Leu Val Gly Ala Gly Ile	395	400	405
	Gly Val Thr Pro Phe Ala Ser Ile Leu Lys Ser Ile Trp Tyr Lys	410	415	420
45	Phe Gln Cys Ala Asp His Asn Leu Lys Thr Lys Lys Val Gly His	425	430	435
	Ala Ala Leu Asn Phe Asp Lys Ala Thr Asp Ile Val Thr Gly Leu	440	445	450
50	Lys Gln Lys Thr Ser Phe Gly Arg Pro Met Trp Asp Asn Glu Phe	455	460	465
55	Ser Thr Ile Ala Thr Ser His Pro Lys Ser Val Val Gly Val Phe			

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					470						475				480
5	Leu	Cys	Gly	Pro	Arg	Thr	Leu	Ala	Lys	Ser	Leu	Arg	Lys	Cys	Cys
					485					490					495
	His	Arg	Tyr	Ser	Ser	Leu	Asp	Pro	Arg	Lys	Val	Gln	Phe	Tyr	Phe
					500					505					510
10	Asn	Lys	Glu	Asn	Phe										
					515										
	<210> 134														
	<211> 757														
	<212> PRT														
15	<213> Homo Sapien														
	<400> 134														
	Met	Thr	Ser	Gly	Ser	Val	Phe	Phe	Tyr	Ile	Leu	Ile	Phe	Gly	Lys
	1				5					10					15
20	Tyr	Phe	Ser	His	Gly	Gly	Gly	Gln	Asp	Val	Lys	Cys	Ser	Leu	Gly
					20					25					30
	Tyr	Phe	Pro	Cys	Gly	Asn	Ile	Thr	Lys	Cys	Leu	Pro	Gln	Leu	Leu
					35					40					45
25	His	Cys	Asn	Gly	Val	Asp	Asp	Cys	Gly	Asn	Gln	Ala	Asp	Glu	Asp
					50					55					60
	Asn	Cys	Gly	Asp	Asn	Asn	Gly	Trp	Ser	Met	Gln	Phe	Asp	Lys	Tyr
					65					70					75
30	Phe	Ala	Ser	Tyr	Tyr	Lys	Met	Thr	Ser	Gln	Tyr	Pro	Phe	Glu	Ala
					80					85					90
	Glu	Thr	Pro	Glu	Cys	Leu	Val	Gly	Ser	Val	Pro	Val	Gln	Cys	Leu
					95					100					105
35	Cys	Gln	Gly	Leu	Glu	Leu	Asp	Cys	Asp	Glu	Thr	Asn	Leu	Arg	Ala
					110					115					120
	Val	Pro	Ser	Val	Ser	Ser	Asn	Val	Thr	Ala	Met	Ser	Leu	Gln	Trp
					125					130					135
40	Asn	Leu	Ile	Arg	Lys	Leu	Pro	Pro	Asp	Cys	Phe	Lys	Asn	Tyr	His
					140					145					150
	Asp	Leu	Gln	Lys	Leu	Tyr	Leu	Gln	Asn	Asn	Lys	Ile	Thr	Ser	Ile
					155					160					165
45	Ser	Ile	Tyr	Ala	Phe	Arg	Gly	Leu	Asn	Ser	Leu	Thr	Lys	Leu	Tyr
					170					175					180
	Leu	Ser	His	Asn	Arg	Ile	Thr	Phe	Leu	Lys	Pro	Gly	Val	Phe	Glu
					185					190					195
50	Asp	Leu	His	Arg	Leu	Glu	Trp	Leu	Ile	Ile	Glu	Asp	Asn	His	Leu
					200					205					210
	Ser	Arg	Ile	Ser	Pro	Pro	Thr	Phe	Tyr	Gly	Leu	Asn	Ser	Leu	Ile
55					215					220					225

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5	Leu Leu Val Leu Met Asn Asn Val Leu Thr Arg Leu Pro Asp Lys	230	235	240
	Pro Leu Cys Gln His Met Pro Arg Leu His Trp Leu Asp Leu Glu	245	250	255
10	Gly Asn His Ile His Asn Leu Arg Asn Leu Thr Phe Ile Ser Cys	260	265	270
	Ser Asn Leu Thr Val Leu Val Met Arg Lys Asn Lys Ile Asn His	275	280	285
15	Leu Asn Glu Asn Thr Phe Ala Pro Leu Gln Lys Leu Asp Glu Leu	290	295	300
	Asp Leu Gly Ser Asn Lys Ile Glu Asn Leu Pro Pro Leu Ile Phe	305	310	315
20	Lys Asp Leu Lys Glu Leu Ser Gln Leu Asn Leu Ser Tyr Asn Pro	320	325	330
	Ile Gln Lys Ile Gln Ala Asn Gln Phe Asp Tyr Leu Val Lys Leu	335	340	345
25	Lys Ser Leu Ser Leu Glu Gly Ile Glu Ile Ser Asn Ile Gln Gln	350	355	360
	Arg Met Phe Arg Pro Leu Met Asn Leu Ser His Ile Tyr Phe Lys	365	370	375
30	Lys Phe Gln Tyr Cys Gly Tyr Ala Pro His Val Arg Ser Cys Lys	380	385	390
	Pro Asn Thr Asp Gly Ile Ser Ser Leu Glu Asn Leu Leu Ala Ser	395	400	405
35	Ile Ile Gln Arg Val Phe Val Trp Val Val Ser Ala Val Thr Cys	410	415	420
	Phe Gly Asn Ile Phe Val Ile Cys Met Arg Pro Tyr Ile Arg Ser	425	430	435
40	Glu Asn Lys Leu Tyr Ala Met Ser Ile Ile Ser Leu Cys Cys Ala	440	445	450
	Asp Cys Leu Met Gly Ile Tyr Leu Phe Val Ile Gly Gly Phe Asp	455	460	465
45	Leu Lys Phe Arg Gly Glu Tyr Asn Lys His Ala Gln Leu Trp Met	470	475	480
	Glu Ser Thr His Cys Gln Leu Val Gly Ser Leu Ala Ile Leu Ser	485	490	495
50	Thr Glu Val Ser Val Leu Leu Leu Thr Phe Leu Thr Leu Glu Lys	500	505	510
55	Tyr Ile Cys Ile Val Tyr Pro Phe Arg Cys Val Arg Pro Gly Lys	515	520	525

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	Cys Arg Thr Ile Thr Val Leu Ile Leu Ile Trp Ile Thr Gly Phe	530	535	540
5	Ile Val Ala Phe Ile Pro Leu Ser Asn Lys Glu Phe Phe Lys Asn	545	550	555
	Tyr Tyr Gly Thr Asn Gly Val Cys Phe Pro Leu His Ser Glu Asp	560	565	570
10	Thr Glu Ser Ile Gly Ala Gln Ile Tyr Ser Val Ala Ile Phe Leu	575	580	585
	Gly Ile Asn Leu Ala Ala Phe Ile Ile Ile Val Phe Ser Tyr Gly	590	595	600
15	Ser Met Phe Tyr Ser Val His Gln Ser Ala Ile Thr Ala Thr Glu	605	610	615
	Ile Arg Asn Gln Val Lys Lys Glu Met Ile Leu Ala Lys Arg Phe	620	625	630
20	Phe Phe Ile Val Phe Thr Asp Ala Leu Cys Trp Ile Pro Ile Phe	635	640	645
	Val Val Lys Phe Leu Ser Leu Leu Gln Val Glu Ile Pro Gly Thr	650	655	660
25	Ile Thr Ser Trp Val Val Ile Phe Ile Leu Pro Ile Asn Ser Ala	665	670	675
	Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Arg Pro Phe Lys Glu	680	685	690
30	Met Ile His Arg Phe Trp Tyr Asn Tyr Arg Gln Arg Lys Ser Met	695	700	705
	Asp Ser Lys Gly Gln Lys Thr Tyr Ala Pro Ser Phe Ile Trp Val	710	715	720
35	Glu Met Trp Pro Leu Gln Glu Met Pro Pro Glu Leu Met Lys Pro	725	730	735
	Asp Leu Phe Thr Tyr Pro Cys Glu Met Ser Leu Ile Ser Gln Ser	740	745	750
	Thr Arg Leu Asn Ser Tyr Ser	755		
45	<210> 135			
	<211> 757			
	<212> PRT			
	<213> Homo Sapien			
	<400> 135			
50	Met Thr Ser Gly Ser Val Phe Phe Tyr Ile Leu Ile Phe Gly Lys	1	5	10
				15
	Tyr Phe Ser His Gly Gly Gly Gln Asp Val Lys Cys Ser Leu Gly	20	25	30
55	Tyr Phe Pro Cys Gly Asn Ile Thr Lys Cys Leu Pro Gln Leu Leu			

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					35					40					45
5	His	Cys	Asn	Gly	Val	Asp	Asp	Cys	Gly	Asn	Gln	Ala	Asp	Glu	Asp
					50					55					60
	Asn	Cys	Gly	Asp	Asn	Asn	Gly	Trp	Ser	Leu	Gln	Phe	Asp	Lys	Tyr
					65					70					75
10	Phe	Ala	Ser	Tyr	Tyr	Lys	Met	Thr	Ser	Gln	Tyr	Pro	Phe	Glu	Ala
					80					85					90
	Glu	Thr	Pro	Glu	Cys	Leu	Val	Gly	Ser	Val	Pro	Val	Gln	Cys	Leu
					95					100					105
15	Cys	Gln	Gly	Leu	Glu	Leu	Asp	Cys	Asp	Glu	Thr	Asn	Leu	Arg	Ala
					110					115					120
	Val	Pro	Ser	Val	Ser	Ser	Asn	Val	Thr	Ala	Met	Ser	Leu	Gln	Trp
					125					130					135
20	Asn	Leu	Ile	Arg	Lys	Leu	Pro	Pro	Asp	Cys	Phe	Lys	Asn	Tyr	His
					140					145					150
	Asp	Leu	Gln	Lys	Leu	Tyr	Leu	Gln	Asn	Asn	Lys	Ile	Thr	Ser	Ile
					155					160					165
25	Ser	Ile	Tyr	Ala	Phe	Arg	Gly	Leu	Asn	Ser	Leu	Thr	Lys	Leu	Tyr
					170					175					180
	Leu	Ser	His	Asn	Arg	Ile	Thr	Phe	Leu	Lys	Pro	Gly	Val	Phe	Glu
					185					190					195
30	Asp	Leu	His	Arg	Leu	Glu	Trp	Leu	Ile	Ile	Glu	Asp	Asn	His	Leu
					200					205					210
	Ser	Arg	Ile	Ser	Pro	Pro	Thr	Phe	Tyr	Gly	Leu	Asn	Ser	Leu	Ile
					215					220					225
35	Leu	Leu	Val	Leu	Met	Asn	Asn	Val	Leu	Thr	Arg	Leu	Pro	Asp	Lys
					230					235					240
	Pro	Leu	Cys	Gln	His	Met	Pro	Arg	Leu	His	Trp	Leu	Asp	Leu	Glu
					245					250					255
40	Gly	Asn	His	Ile	His	Asn	Leu	Arg	Asn	Leu	Thr	Phe	Ile	Ser	Cys
					260					265					270
	Ser	Asn	Leu	Thr	Val	Leu	Val	Met	Arg	Lys	Asn	Lys	Ile	Asn	His
					275					280					285
45	Leu	Asn	Glu	Asn	Thr	Phe	Ala	Pro	Leu	Gln	Lys	Leu	Asp	Glu	Leu
					290					295					300
	Asp	Leu	Gly	Ser	Asn	Lys	Ile	Glu	Asn	Leu	Pro	Pro	Leu	Ile	Phe
					305					310					315
50	Lys	Asp	Leu	Lys	Glu	Leu	Ser	Gln	Leu	Asn	Leu	Ser	Tyr	Asn	Pro
					320					325					330
55	Ile	Gln	Lys	Ile	Gln	Ala	Asn	Gln	Phe	Asp	Tyr	Leu	Val	Lys	Leu
					335					340					345

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5	Lys Ser Leu Ser	Leu Glu Gly Ile Glu Ile Ser Asn Ile Gln Gln	350	355	360
	Arg Met Phe Arg	Pro Leu Met Asn Leu Ser His Ile Tyr Phe Lys	365	370	375
10	Lys Phe Gln Tyr	Cys Gly Tyr Ala Pro His Val Arg Ser Cys Lys	380	385	390
	Pro Asn Thr Asp	Gly Ile Ser Ser Leu Glu Asn Leu Leu Ala Ser	395	400	405
15	Ile Ile Gln Arg	Val Phe Val Trp Val Val Ser Ala Val Thr Cys	410	415	420
	Phe Gly Asn Ile	Phe Val Ile Cys Met Arg Pro Tyr Ile Arg Ser	425	430	435
20	Glu Asn Lys Leu	Tyr Ala Met Ser Ile Ile Ser Leu Cys Cys Ala	440	445	450
	Asp Cys Leu Met	Gly Ile Tyr Leu Phe Val Ile Gly Gly Phe Asp	455	460	465
25	Leu Lys Phe Arg	Gly Glu Tyr Asn Lys His Ala Gln Leu Trp Met	470	475	480
	Glu Ser Thr His	Cys Gln Leu Val Gly Ser Leu Ala Ile Leu Ser	485	490	495
30	Thr Glu Val Ser	Val Leu Leu Leu Thr Phe Leu Thr Leu Glu Lys	500	505	510
	Tyr Ile Cys Ile	Val Tyr Pro Phe Arg Cys Val Arg Pro Gly Lys	515	520	525
35	Cys Arg Thr Ile	Thr Val Leu Ile Leu Ile Trp Ile Thr Gly Phe	530	535	540
	Ile Val Ala Phe	Ile Pro Leu Ser Asn Lys Glu Phe Phe Lys Asn	545	550	555
40	Tyr Tyr Gly Thr	Asn Gly Val Cys Phe Pro Leu His Ser Glu Asp	560	565	570
	Thr Glu Ser Ile	Gly Ala Gln Ile Tyr Ser Val Ala Ile Phe Leu	575	580	585
45	Gly Ile Asn Leu	Ala Ala Phe Ile Ile Ile Val Phe Ser Tyr Gly	590	595	600
	Ser Met Phe Tyr	Ser Val His Gln Ser Ala Ile Thr Ala Thr Glu	605	610	615
50	Ile Arg Asn Gln	Val Lys Lys Glu Met Ile Leu Ala Lys Arg Phe	620	625	630
	Phe Phe Ile Val	Phe Thr Asp Ala Leu Cys Trp Ile Pro Ile Phe	635	640	645
55					

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	Val	Val	Lys	Phe	Leu	Ser	Leu	Leu	Gln	Val	Glu	Ile	Pro	Gly	Thr	
					650					655					660	
5	Ile	Thr	Ser	Trp	Val	Val	Ile	Phe	Ile	Leu	Pro	Ile	Asn	Ser	Ala	
					665					670					675	
	Leu	Asn	Pro	Ile	Leu	Tyr	Thr	Leu	Thr	Thr	Arg	Pro	Phe	Lys	Glu	
					680					685					690	
10	Met	Ile	His	Arg	Phe	Trp	Tyr	Asn	Tyr	Arg	Gln	Arg	Lys	Ser	Met	
					695					700					705	
	Asp	Ser	Lys	Gly	Gln	Lys	Thr	Tyr	Ala	Pro	Ser	Phe	Ile	Trp	Val	
					710					715					720	
15	Glu	Met	Trp	Pro	Leu	Gln	Glu	Met	Pro	Pro	Glu	Leu	Met	Lys	Pro	
					725					730					735	
	Asp	Leu	Phe	Thr	Tyr	Pro	Cys	Glu	Met	Ser	Leu	Ile	Ser	Gln	Ser	
					740					745					750	
20	Thr	Arg	Leu	Asn	Ser	Tyr	Ser									
					755											
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	<211> 879															
25	<212> PRT															
	<213> Homo Sapien															
	<400> 136															
30	Met	Gly	Arg	Leu	Ala	Ser	Arg	Pro	Leu	Leu	Leu	Ala	Leu	Leu	Ser	
	1				5					10					15	
	Leu	Ala	Leu	Cys	Arg	Gly	Arg	Val	Val	Arg	Val	Pro	Thr	Ala	Thr	
					20					25					30	
35	Leu	Val	Arg	Val	Val	Gly	Thr	Glu	Leu	Val	Ile	Pro	Cys	Asn	Val	
					35					40					45	
	Ser	Asp	Tyr	Asp	Gly	Pro	Ser	Glu	Gln	Asn	Phe	Asp	Trp	Ser	Phe	
					50					55					60	
40	Ser	Ser	Leu	Gly	Ser	Ser	Phe	Val	Glu	Leu	Ala	Ser	Thr	Trp	Glu	
					65					70					75	
	Val	Gly	Phe	Pro	Ala	Gln	Leu	Tyr	Gln	Glu	Arg	Leu	Gln	Arg	Gly	
					80					85					90	
45	Glu	Ile	Leu	Leu	Arg	Arg	Thr	Ala	Asn	Asp	Ala	Val	Glu	Leu	His	
					95					100					105	
	Ile	Lys	Asn	Val	Gln	Pro	Ser	Asp	Gln	Gly	His	Tyr	Lys	Cys	Ser	
					110					115					120	
50	Thr	Pro	Ser	Thr	Asp	Ala	Thr	Val	Gln	Gly	Asn	Tyr	Glu	Asp	Thr	
					125					130					135	
	Val	Gln	Val	Lys	Val	Leu	Ala	Asp	Ser	Leu	His	Val	Gly	Pro	Ser	
					140					145					150	
55	Ala	Arg	Pro	Pro	Pro	Ser	Leu	Ser	Leu	Arg	Glu	Gly	Glu	Pro	Phe	

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					155						160					165
5		Glu	Leu	Arg	Cys	Thr	Ala	Ala	Ser	Ala	Ser	Pro	Leu	His	Thr	His
						170					175					180
		Leu	Ala	Leu	Leu	Trp	Glu	Val	His	Arg	Gly	Pro	Ala	Arg	Arg	Ser
						185					190					195
10		Val	Leu	Ala	Leu	Thr	His	Glu	Gly	Arg	Phe	His	Pro	Gly	Leu	Gly
						200					205					210
		Tyr	Glu	Gln	Arg	Tyr	His	Ser	Gly	Asp	Val	Arg	Leu	Asp	Thr	Val
						215					220					225
15		Gly	Ser	Asp	Ala	Tyr	Arg	Leu	Ser	Val	Ser	Arg	Ala	Leu	Ser	Ala
						230					235					240
		Asp	Gln	Gly	Ser	Tyr	Arg	Cys	Ile	Val	Ser	Glu	Trp	Ile	Ala	Glu
						245					250					255
20		Gln	Gly	Asn	Trp	Gln	Glu	Ile	Gln	Glu	Lys	Ala	Val	Glu	Val	Ala
						260					265					270
		Thr	Val	Val	Ile	Gln	Pro	Thr	Val	Leu	Arg	Ala	Ala	Val	Pro	Lys
						275					280					285
25		Asn	Val	Ser	Val	Ala	Glu	Gly	Lys	Glu	Leu	Asp	Leu	Thr	Cys	Asn
						290					295					300
		Ile	Thr	Thr	Asp	Arg	Ala	Asp	Asp	Val	Arg	Pro	Glu	Val	Thr	Trp
						305					310					315
30		Ser	Phe	Ser	Arg	Met	Pro	Asp	Ser	Thr	Leu	Pro	Gly	Ser	Arg	Val
						320					325					330
		Leu	Ala	Arg	Leu	Asp	Arg	Asp	Ser	Leu	Val	His	Ser	Ser	Pro	His
						335					340					345
35		Val	Ala	Leu	Ser	His	Val	Asp	Ala	Arg	Ser	Tyr	His	Leu	Leu	Val
						350					355					360
		Arg	Asp	Val	Ser	Lys	Glu	Asn	Ser	Gly	Tyr	Tyr	Tyr	Cys	His	Val
						365					370					375
40		Ser	Leu	Trp	Ala	Pro	Gly	His	Asn	Arg	Ser	Trp	His	Lys	Val	Ala
						380					385					390
		Glu	Ala	Val	Ser	Ser	Pro	Ala	Gly	Val	Gly	Val	Thr	Trp	Leu	Glu
						395					400					405
45		Pro	Asp	Tyr	Gln	Val	Tyr	Leu	Asn	Ala	Ser	Lys	Val	Pro	Gly	Phe
						410					415					420
		Ala	Asp	Asp	Pro	Thr	Glu	Leu	Ala	Cys	Arg	Val	Val	Asp	Thr	Lys
						425					430					435
50		Ser	Gly	Glu	Ala	Asn	Val	Arg	Phe	Thr	Val	Ser	Trp	Tyr	Tyr	Arg
						440					445					450
55		Met	Asn	Arg	Arg	Ser	Asp	Asn	Val	Val	Thr	Ser	Glu	Leu	Leu	Ala
						455					460					465

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5	Val Met Asp Gly Asp Trp Thr Leu Lys Tyr Gly Glu Arg Ser Lys	470	475	480
	Gln Arg Ala Gln Asp Gly Asp Phe Ile Phe Ser Lys Glu His Thr	485	490	495
10	Asp Thr Phe Asn Phe Arg Ile Gln Arg Thr Thr Glu Glu Asp Arg	500	505	510
	Gly Asn Tyr Tyr Cys Val Val Ser Ala Trp Thr Lys Gln Arg Asn	515	520	525
15	Asn Ser Trp Val Lys Ser Lys Asp Val Phe Ser Lys Pro Val Asn	530	535	540
	Ile Phe Trp Ala Leu Glu Asp Ser Val Leu Val Val Lys Ala Arg	545	550	555
20	Gln Pro Lys Pro Phe Phe Ala Ala Gly Asn Thr Phe Glu Met Thr	560	565	570
	Cys Lys Val Ser Ser Lys Asn Ile Lys Ser Pro Arg Tyr Ser Val	575	580	585
25	Leu Ile Met Ala Glu Lys Pro Val Gly Asp Leu Ser Ser Pro Asn	590	595	600
	Glu Thr Lys Tyr Ile Ile Ser Leu Asp Gln Asp Ser Val Val Lys	605	610	615
30	Leu Glu Asn Trp Thr Asp Ala Ser Arg Val Asp Gly Val Val Leu	620	625	630
	Glu Lys Val Gln Glu Asp Glu Phe Arg Tyr Arg Met Tyr Gln Thr	635	640	645
35	Gln Val Ser Asp Ala Gly Leu Tyr Arg Cys Met Val Thr Ala Trp	650	655	660
	Ser Pro Val Arg Gly Ser Leu Trp Arg Glu Ala Ala Thr Ser Leu	665	670	675
40	Ser Asn Pro Ile Glu Ile Asp Phe Gln Thr Ser Gly Pro Ile Phe	680	685	690
	Asn Ala Ser Val His Ser Asp Thr Pro Ser Val Ile Arg Gly Asp	695	700	705
45	Leu Ile Lys Leu Phe Cys Ile Ile Thr Val Glu Gly Ala Ala Leu	710	715	720
	Asp Pro Asp Asp Met Ala Phe Asp Val Ser Trp Phe Ala Val His	725	730	735
50	Ser Phe Gly Leu Asp Lys Ala Pro Val Leu Leu Ser Ser Leu Asp	740	745	750
55	Arg Lys Gly Ile Val Thr Thr Ser Arg Arg Asp Trp Lys Ser Asp	755	760	765

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	Leu Ser Leu Glu Arg Val Ser Val Leu Glu Phe Leu Leu Gln Val	770	775	780
5	His Gly Ser Glu Asp Gln Asp Phe Gly Asn Tyr Tyr Cys Ser Val	785	790	795
	Thr Pro Trp Val Lys Ser Pro Thr Gly Ser Trp Gln Lys Glu Ala	800	805	810
10	Glu Ile His Ser Lys Pro Val Phe Ile Thr Val Lys Met Asp Val	815	820	825
	Leu Asn Ala Phe Lys Tyr Pro Leu Leu Ile Gly Ile Gly Leu Ser	830	835	840
15	Thr Val Ile Gly Leu Leu Ser Cys Leu Ile Gly Tyr Cys Ser Ser	845	850	855
	His Trp Cys Cys Lys Lys Glu Val Gln Glu Thr Arg Arg Glu Arg	860	865	870
20	Arg Arg Leu Met Ser Met Glu Met Asp	875		
	<210> 137			
25	<211> 434			
	<212> PRT			
	<213> Homo Sapien			
	<400> 137			
30	Met Ser Arg Ser Arg His Leu Gly Lys Ile Arg Lys Arg Leu Glu	1	5	10
	Asp Val Lys Ser Gln Trp Val Arg Pro Ala Arg Ala Asp Phe Ser	20	25	30
35	Asp Asn Glu Ser Ala Arg Leu Ala Thr Asp Ala Leu Leu Asp Gly	35	40	45
	Gly Ser Glu Ala Tyr Trp Arg Val Leu Ser Gln Glu Gly Glu Val	50	55	60
40	Asp Phe Leu Ser Ser Val Glu Ala Gln Tyr Ile Gln Ala Gln Ala	65	70	75
	Arg Glu Pro Pro Cys Pro Pro Asp Thr Leu Gly Gly Ala Glu Ala	80	85	90
45	Gly Pro Lys Gly Leu Asp Ser Ser Ser Leu Gln Ser Gly Thr Tyr	95	100	105
	Phe Pro Val Ala Ser Glu Gly Ser Glu Pro Ala Leu Leu His Ser	110	115	120
50	Trp Ala Ser Ala Glu Lys Pro Tyr Leu Lys Glu Lys Ser Ser Ala	125	130	135
	Thr Val Tyr Phe Gln Thr Val Lys His Asn Asn Ile Arg Asp Leu	140	145	150
55	Val Arg Arg Cys Ile Thr Arg Thr Ser Gln Val Leu Val Ile Leu			

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		155		160		165
5	Met Asp Val Phe Thr Asp Val Glu Ile Phe Cys Asp Ile Leu Glu	170		175		180
	Ala Ala Asn Lys Arg Gly Val Phe Val Cys Val Leu Leu Asp Gln	185		190		195
10	Gly Gly Val Lys Leu Phe Gln Glu Met Cys Asp Lys Val Gln Ile	200		205		210
	Ser Asp Ser His Leu Lys Asn Ile Ser Ile Arg Ser Val Glu Gly	215		220		225
15	Glu Ile Tyr Cys Ala Lys Ser Gly Arg Lys Phe Ala Gly Gln Ile	230		235		240
	Arg Glu Lys Phe Ile Ile Ser Asp Trp Arg Phe Val Leu Ser Gly	245		250		255
20	Ser Tyr Ser Phe Thr Trp Leu Cys Gly His Val His Arg Asn Ile	260		265		270
	Leu Ser Lys Phe Thr Gly Gln Ala Val Glu Leu Phe Asp Glu Glu	275		280		285
25	Phe Arg His Leu Tyr Ala Ser Ser Lys Pro Val Met Gly Leu Lys	290		295		300
	Ser Pro Arg Leu Val Ala Pro Val Pro Pro Gly Ala Ala Pro Ala	305		310		315
30	Asn Gly Arg Leu Ser Ser Ser Ser Gly Ser Ala Ser Asp Arg Thr	320		325		330
	Ser Ser Asn Pro Phe Ser Gly Arg Ser Ala Gly Ser His Pro Gly	335		340		345
35	Thr Arg Ser Val Ser Ala Ser Ser Gly Pro Cys Ser Pro Ala Ala	350		355		360
	Pro His Pro Pro Pro Pro Pro Arg Phe Gln Pro His Gln Gly Pro	365		370		375
40	Trp Gly Ala Pro Ser Pro Gln Ala His Leu Ser Pro Arg Pro His	380		385		390
	Asp Gly Pro Pro Ala Ala Val Tyr Ser Asn Leu Gly Ala Tyr Arg	395		400		405
45	Pro Thr Arg Leu Gln Leu Glu Gln Leu Gly Leu Val Pro Arg Leu	410		415		420
	Thr Pro Thr Trp Arg Pro Phe Leu Gln Ala Ser Pro His Phe	425		430		
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<400> 138

5	Met	Ala	Leu	Pro	Gln	Pro	Pro	Pro	Pro	Ala	Gly	Ala	Arg	Asp	Pro	1	5	10	15
	Val	Thr	Pro	Glu	His	Trp	Ala	Ser	Gly	Pro	Pro	Ser	Gln	Ala	Gln	20	25	30	
10	Pro	Leu	Leu	Arg	Gln	Glu	Ala	Lys	Glu	Glu	Glu	Glu	Gly	Glu	Glu	35	40	45	
	Thr	Gly	Val	Gln	Gly	Ala	Trp	Gly	Thr	Gly	Thr	Ala	Glu	Gln	Arg	50	55	60	
15	Arg	Arg	Gly	Trp	Gly	Glu	Ala	Ala	Glu	Ser	Ala	Ala	Ala	Glu	Glu	65	70	75	
	Gly	Gln	Ala	Glu	Val	Gly	Gly	Ala	Ala	Ala	Ala	Gly	Ser	Gly	Ser	80	85	90	
20	Pro	Ala	Gly	Gly	Ala	Gly	Gly	Gly	Leu	Gly	Ser	Trp	Arg	Pro	Leu	95	100	105	
	Leu	Ala	Trp	Leu	Gln	Arg	Arg	Gln	Pro	Gln	Cys	Cys	Pro	Cys	Ala	110	115	120	
25	Ala	Pro	Leu	Ser	Arg	Ser	Ala	Ala	His	Cys	Cys	His	Gly	Gly	Thr	125	130	135	
	Lys	Met	Ala	Ala	Leu	Ala	Tyr	Asn	Leu	Gly	Lys	Arg	Glu	Ile	Asn	140	145	150	
30	His	Tyr	Phe	Ser	Val	Arg	Ser	Ala	Lys	Val	Leu	Ala	Leu	Val	Ala	155	160	165	
	Val	Leu	Leu	Leu	Ala	Ala	Cys	His	Leu	Ala	Ser	Arg	Arg	Tyr	Arg	170	175	180	
35	Gly	Asn	Asp	Ser	Cys	Glu	Tyr	Leu	Leu	Ser	Ser	Gly	Arg	Phe	Leu	185	190	195	
	Gly	Glu	Lys	Val	Trp	Gln	Pro	His	Ser	Cys	Met	Met	His	Lys	Tyr	200	205	210	
40	Lys	Ile	Ser	Glu	Ala	Lys	Asn	Cys	Leu	Val	Asp	Lys	His	Ile	Ala	215	220	225	
	Phe	Ile	Gly	Asp	Ser	Arg	Ile	Arg	Gln	Leu	Phe	Tyr	Ser	Phe	Val	230	235	240	
45	Lys	Ile	Ile	Asn	Pro	Gln	Phe	Lys	Glu	Glu	Gly	Asn	Lys	His	Glu	245	250	255	
	Asn	Ile	Pro	Phe	Glu	Asp	Lys	Thr	Ala	Ser	Val	Lys	Val	Asp	Phe	260	265	270	
50	Leu	Trp	His	Pro	Glu	Val	Asn	Gly	Ser	Met	Lys	Gln	Cys	Ile	Lys	275	280	285	
55	Val	Trp	Thr	Glu	Asp	Ser	Ile	Ala	Lys	Pro	His	Val	Ile	Val	Ala	290	295	300	

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	Gly Ala Ala Thr Trp Ser Ile Lys Ile His Asn Gly Ser Ser Glu	305	310	315
5	Ala Leu Ser Gln Tyr Lys Met Asn Ile Thr Ser Ile Ala Pro Leu	320	325	330
	Leu Glu Lys Leu Ala Lys Thr Ser Asp Val Tyr Trp Val Leu Gln	335	340	345
10	Asp Pro Val Tyr Glu Asp Leu Leu Ser Glu Asn Arg Lys Met Ile	350	355	360
	Thr Asn Glu Lys Ile Asp Ala Tyr Asn Glu Ala Ala Val Ser Ile	365	370	375
15	Leu Asn Ser Ser Thr Arg Asn Ser Lys Ser Asn Val Lys Met Phe	380	385	390
	Ser Val Ser Lys Leu Ile Ala Gln Glu Thr Ile Met Glu Ser Leu	395	400	405
20	Asp Gly Leu His Leu Pro Glu Ser Ser Arg Glu Thr Thr Ala Met	410	415	420
	Ile Leu Met Asn Val Tyr Cys Asn Lys Ile Leu Lys Pro Val Asp	425	430	435
25	Gly Ser Cys Cys Gln Pro Arg Pro Pro Val Thr Leu Ile Gln Lys	440	445	450
	Leu Ala Ala Cys Phe Phe Thr Leu Ser Ile Ile Gly Tyr Leu Ile	455	460	465
30	Phe Tyr Ile Ile His Arg Asn Ala His Arg Lys Asn Lys Pro Cys	470	475	480
	Thr Asp Leu Glu Ser Gly Glu Glu Lys Lys Asn Ile Ile Asn Thr	485	490	495
35	Pro Val Ser Ser Leu Glu Ile Leu Leu Gln Ser Phe Cys Lys Leu	500	505	510
	Gly Leu Ile Met Ala Tyr Phe Tyr Met Cys Asp Arg Ala Asn Leu	515	520	525
40	Phe Met Lys Glu Asn Lys Phe Tyr Thr His Ser Ser Phe Phe Ile	530	535	540
	Pro Ile Ile Tyr Ile Leu Val Leu Gly Val Phe Tyr Asn Glu Asn	545	550	555
45	Thr Lys Glu Thr Lys Val Leu Asn Arg Glu Gln Thr Asp Glu Trp	560	565	570
	Lys Gly Trp Met Gln Leu Val Ile Leu Ile Tyr His Ile Ser Gly	575	580	585
50	Ala Ser Thr Phe Leu Pro Val Tyr Met His Ile Arg Val Leu Val	590	595	600
55	Ala Ala Tyr Leu Phe Gln Thr Gly Tyr Gly His Phe Ser Tyr Phe			

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					605					610					615
5	Trp	Ile	Lys	Gly	Asp 620	Phe	Gly	Ile	Tyr	Arg 625	Val	Cys	Gln	Val	Leu 630
	Phe	Arg	Leu	Asn	Phe 635	Leu	Val	Val	Val	Leu 640	Cys	Ile	Val	Met	Asp 645
10	Arg	Pro	Tyr	Gln	Phe 650	Tyr	Tyr	Phe	Val	Pro 655	Leu	Val	Thr	Val	Trp 660
	Phe	Met	Val	Ile	Tyr 665	Val	Thr	Leu	Ala	Leu 670	Trp	Pro	Gln	Ile	Ile 675
15	Gln	Lys	Lys	Ala	Asn 680	Gly	Asn	Cys	Phe	Trp 685	His	Phe	Gly	Leu	Leu 690
	Leu	Lys	Leu	Gly	Phe 695	Leu	Leu	Leu	Phe	Ile 700	Cys	Phe	Leu	Ala	Tyr 705
20	Ser	Gln	Gly	Ala	Phe 710	Glu	Lys	Ile	Phe	Ser 715	Leu	Trp	Pro	Leu	Ser 720
	Lys	Cys	Phe	Glu	Leu 725	Lys	Gly	Asn	Val	Tyr 730	Glu	Trp	Trp	Phe	Arg 735
25	Trp	Arg	Leu	Asp	Arg 740	Tyr	Val	Val	Phe	His 745	Gly	Met	Leu	Phe	Ala 750
	Phe	Ile	Tyr	Leu	Ala 755	Leu	Gln	Lys	Arg	Gln 760	Ile	Leu	Ser	Glu	Gly 765
30	Lys	Gly	Glu	Pro	Leu 770	Phe	Ser	Asn	Lys	Ile 775	Ser	Asn	Phe	Leu	Leu 780
	Phe	Ile	Ser	Val	Val 785	Ser	Phe	Leu	Thr	Tyr 790	Ser	Ile	Trp	Ala	Ser 795
35	Ser	Cys	Lys	Asn	Lys 800	Ala	Glu	Cys	Asn	Glu 805	Leu	His	Pro	Ser	Val 810
	Ser	Val	Val	Gln	Ile 815	Leu	Ala	Phe	Ile	Leu 820	Ile	Arg	Asn	Ile	Pro 825
40	Gly	Tyr	Ala	Arg	Ser 830	Val	Tyr	Ser	Ser	Phe 835	Phe	Ala	Trp	Phe	Gly 840
	Lys	Ile	Ser	Leu	Glu 845	Leu	Phe	Ile	Cys	Gln 850	Tyr	His	Ile	Trp	Leu 855
45	Ala	Ala	Asp	Thr	Arg 860	Gly	Ile	Leu	Val	Leu 865	Ile	Pro	Gly	Asn	Pro 870
	Met	Leu	Asn	Ile	Ile 875	Val	Ser	Thr	Phe	Ile 880	Phe	Val	Cys	Val	Ala 885
50	His	Glu	Ile	Ser	Gln 890	Ile	Thr	Asn	Asp	Leu 895	Ala	Gln	Ile	Ile	Ile 900
55	Pro	Lys	Asp	Asn	Ser 905	Ser	Leu	Leu	Lys	Arg 910	Leu	Ala	Cys	Ile	Ala 915

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Ala Phe Phe Cys Gly Leu Leu Ile Leu Ser Ser Ile Gln Asp Lys
920 925 930

5 Ser Lys His

<210> 139
<211> 320
10 <212> PRT
<213> Homo Sapien

<400> 139
Met Tyr His Cys His Ser Gly Ser Lys Pro Thr Glu Lys Gly Ala
15 1 5 10 15

Asn Glu Tyr Ala Tyr Ala Lys Trp Lys Leu Cys Ser Ala Ser Ala
20 20 25 30

Ile Cys Phe Ile Phe Met Ile Ala Glu Val Val Gly Gly His Ile
35 40 45

Ala Gly Ser Leu Ala Val Val Thr Asp Ala Ala His Leu Leu Ile
50 55 60

Asp Leu Thr Ser Phe Leu Leu Ser Leu Phe Ser Leu Trp Leu Ser
25 65 70 75

Ser Lys Pro Pro Ser Lys Arg Leu Thr Phe Gly Trp His Arg Ala
80 85 90

Glu Ile Leu Gly Ala Leu Leu Ser Ile Leu Cys Ile Trp Val Val
30 95 100 105

Thr Gly Val Leu Val Tyr Leu Ala Cys Glu Arg Leu Leu Tyr Pro
110 115 120

Asp Tyr Gln Ile Gln Ala Thr Val Met Ile Ile Val Ser Ser Cys
35 125 130 135

Ala Val Ala Ala Asn Ile Val Leu Thr Val Val Leu His Gln Arg
140 145 150

Cys Leu Gly His Asn His Lys Glu Val Gln Ala Asn Ala Ser Val
40 155 160 165

Arg Ala Ala Phe Val His Ala Leu Gly Asp Leu Phe Gln Ser Ile
170 175 180

Ser Val Leu Ile Ser Ala Leu Ile Ile Tyr Phe Lys Pro Glu Tyr
45 185 190 195

Lys Ile Ala Asp Pro Ile Cys Thr Phe Ile Phe Ser Ile Leu Val
200 205 210

Leu Ala Ser Thr Ile Thr Ile Leu Lys Asp Phe Ser Ile Leu Leu
50 215 220 225

Met Glu Gly Val Pro Lys Ser Leu Asn Tyr Ser Gly Val Lys Glu
230 235 240

55

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	Leu Ile Leu Ala Val Asp Gly Val Leu Ser Val His Ser Leu His	245	250	255
5	Ile Trp Ser Leu Thr Met Asn Gln Val Ile Leu Ser Ala His Val	260	265	270
	Ala Thr Ala Ala Ser Arg Asp Ser Gln Val Val Arg Arg Glu Ile	275	280	285
10	Ala Lys Ala Leu Ser Lys Ser Phe Thr Met His Ser Leu Thr Ile	290	295	300
	Gln Met Glu Ser Pro Val Asp Gln Asp Pro Asp Cys Leu Phe Cys	305	310	315
15	Glu Asp Pro Cys Asp	320		
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20	<212> PRT			
	<213> Homo Sapien			
	<400> 140			
25	Met Val Leu Ser Val Pro Val Ile Ala Leu Gly Ala Thr Leu Gly	1	5	10
	Thr Ala Thr Ser Ile Leu Ala Leu Cys Gly Val Thr Cys Leu Cys	20	25	30
30	Arg His Met His Pro Lys Lys Gly Leu Leu Pro Arg Asp Gln Asp	35	40	45
	Pro Asp Leu Glu Lys Ala Lys Pro Ser Leu Leu Gly Ser Ala Gln	50	55	60
35	Gln Phe Asn Val Lys Lys Ser Thr Glu Pro Val Gln Pro Arg Ala	65	70	75
	Leu Leu Lys Phe Pro Asp Ile Tyr Gly Pro Arg Pro Ala Val Thr	80	85	90
40	Ala Pro Glu Val Ile Asn Tyr Ala Asp Tyr Ser Leu Arg Ser Thr	95	100	105
	Glu Glu Pro Thr Ala Pro Ala Ser Pro Gln Pro Pro Asn Asp Ser	110	115	120
45	Arg Leu Lys Arg Gln Val Thr Glu Glu Leu Phe Ile Leu Pro Gln	125	130	135
	Asn Gly Val Val Glu Asp Val Cys Val Met Glu Thr Trp Asn Pro	140	145	150
50	Glu Lys Ala Ala Ser Trp Asn Gln Ala Pro Lys Leu His Tyr Cys	155	160	165
	Leu Asp Tyr Asp Cys Gln Lys Ala Glu Leu Phe Val Thr Arg Leu	170	175	180
55	Glu Ala Val Thr Ser Asn His Asp Gly Gly Cys Asp Cys Tyr Val			

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					185					190				195	
5	Gln	Gly	Ser	Val	Ala	Asn	Arg	Thr	Gly	Ser	Val	Glu	Ala	Gln	Thr
					200					205				210	
	Ala	Leu	Lys	Lys	Arg	Gln	Leu	His	Thr	Thr	Trp	Glu	Glu	Gly	Leu
					215					220				225	
10	Val	Leu	Pro	Leu	Ala	Glu	Glu	Glu	Leu	Pro	Thr	Ala	Thr	Leu	Thr
					230					235				240	
	Leu	Thr	Leu	Arg	Thr	Cys	Asp	Arg	Phe	Ser	Arg	His	Ser	Val	Ala
					245					250				255	
15	Gly	Glu	Leu	Arg	Leu	Gly	Leu	Asp	Gly	Thr	Ser	Val	Pro	Leu	Gly
					260					265				270	
	Ala	Ala	Gln	Trp	Gly	Glu	Leu	Lys	Thr	Ser	Ala	Lys	Glu	Pro	Ser
					275					280				285	
20	Ala	Gly	Ala	Gly	Glu	Val	Leu	Leu	Ser	Ile	Ser	Tyr	Leu	Pro	Ala
					290					295				300	
	Ala	Asn	Arg	Leu	Leu	Val	Val	Leu	Ile	Lys	Ala	Lys	Asn	Leu	His
					305					310				315	
25	Ser	Asn	Gln	Ser	Lys	Glu	Leu	Leu	Gly	Lys	Asp	Val	Ser	Val	Lys
					320					325				330	
	Val	Thr	Leu	Lys	His	Gln	Ala	Arg	Lys	Leu	Lys	Lys	Lys	Gln	Thr
					335					340				345	
30	Lys	Arg	Ala	Lys	His	Lys	Ile	Asn	Pro	Val	Trp	Asn	Glu	Met	Ile
					350					355				360	
	Met	Phe	Glu	Leu	Pro	Asp	Asp	Leu	Leu	Gln	Ala	Ser	Ser	Val	Glu
					365					370				375	
35	Leu	Glu	Val	Leu	Gly	Gln	Asp	Asp	Ser	Gly	Gln	Ser	Cys	Ala	Leu
					380					385				390	
	Gly	His	Cys	Ser	Leu	Gly	Leu	His	Thr	Ser	Gly	Ser	Glu	Arg	Ser
					395					400				405	
40	His	Trp	Glu	Glu	Met	Leu	Lys	Asn	Pro	Arg	Arg	Gln	Ile	Ala	Met
					410					415				420	
	Trp	His	Gln	Leu	His	Leu									
45					425										
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	<213> Homo Sapien														
50	<400> 141														
	Met	Gln	Lys	Ile	Met	His	Ile	Ser	Val	Leu	Leu	Ser	Pro	Val	Leu
	1				5					10				15	
55	Trp	Gly	Leu	Ile	Phe	Gly	Val	Ser	Ser	Asn	Ser	Ile	Gln	Ile	Gly
					20					25				30	

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5	Gly Leu Phe Pro Arg Gly Ala Asp Gln Glu Tyr Ser Ala Phe Arg	35	40	45
	Val Gly Met Val Gln Phe Ser Thr Ser Glu Phe Arg Leu Thr Pro	50	55	60
10	His Ile Asp Asn Leu Glu Val Ala Asn Ser Phe Ala Val Thr Asn	65	70	75
	Ala Phe Cys Ser Gln Phe Ser Arg Gly Val Tyr Ala Ile Phe Gly	80	85	90
15	Phe Tyr Asp Lys Lys Ser Val Asn Thr Ile Thr Ser Phe Cys Gly	95	100	105
	Thr Leu His Val Ser Phe Ile Thr Pro Ser Phe Pro Thr Asp Gly	110	115	120
20	Thr His Pro Phe Val Ile Gln Met Arg Pro Asp Leu Lys Gly Ala	125	130	135
	Leu Leu Ser Leu Ile Glu Tyr Tyr Gln Trp Asp Lys Phe Ala Tyr	140	145	150
25	Leu Tyr Asp Ser Asp Arg Gly Leu Ser Thr Leu Gln Ala Val Leu	155	160	165
	Asp Ser Ala Ala Glu Lys Lys Trp Gln Val Thr Ala Ile Asn Val	170	175	180
30	Gly Asn Ile Asn Asn Asp Lys Lys Asp Glu Met Tyr Arg Ser Leu	185	190	195
	Phe Gln Asp Leu Glu Leu Lys Lys Glu Arg Arg Val Ile Leu Asp	200	205	210
35	Cys Glu Arg Asp Lys Val Asn Asp Ile Val Asp Gln Val Ile Thr	215	220	225
	Ile Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala Asn Leu	230	235	240
40	Glu Phe Thr Asp Gly Asp Leu Leu Lys Ile Gln Phe Gly Gly Ala	245	250	255
	Asn Val Ser Gly Phe Gln Ile Val Asp Tyr Asp Asp Ser Leu Val	260	265	270
45	Ser Lys Phe Ile Glu Arg Trp Ser Thr Leu Glu Glu Lys Glu Tyr	275	280	285
	Pro Gly Ala His Thr Thr Thr Ile Lys Tyr Thr Ser Ala Leu Thr	290	295	300
50	Tyr Asp Ala Val Gln Val Met Thr Glu Ala Phe Arg Asn Leu Arg	305	310	315
55	Lys Gln Arg Ile Glu Ile Ser Arg Arg Gly Asn Ala Gly Asp Cys	320	325	330

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	Leu	Ala	Asn	Pro	Ala	Val	Pro	Trp	Gly	Gln	Gly	Val	Glu	Ile	Glu	
					335					340					345	
5	Arg	Ala	Leu	Lys	Gln	Val	Gln	Val	Glu	Gly	Leu	Ser	Gly	Asn	Ile	
					350					355					360	
	Lys	Phe	Asp	Gln	Asn	Gly	Lys	Arg	Ile	Asn	Tyr	Thr	Ile	Asn	Ile	
					365					370					375	
10	Met	Glu	Leu	Lys	Thr	Asn	Gly	Pro	Arg	Lys	Ile	Gly	Tyr	Trp	Ser	
					380					385					390	
	Glu	Val	Asp	Lys	Met	Val	Val	Thr	Leu	Thr	Glu	Leu	Pro	Ser	Gly	
					395					400					405	
15	Asn	Asp	Thr	Ser	Gly	Leu	Glu	Asn	Lys	Thr	Val	Val	Val	Thr	Thr	
					410					415					420	
	Ile	Leu	Glu	Ser	Pro	Tyr	Val	Met	Met	Lys	Lys	Asn	His	Glu	Met	
					425					430					435	
20	Leu	Glu	Gly	Asn	Glu	Arg	Tyr	Glu	Gly	Tyr	Cys	Val	Asp	Leu	Ala	
					440					445					450	
	Ala	Glu	Ile	Ala	Lys	His	Cys	Gly	Phe	Lys	Tyr	Lys	Leu	Thr	Ile	
25					455					460					465	
	Val	Gly	Asp	Gly	Lys	Tyr	Gly	Ala	Arg	Asp	Ala	Asp	Thr	Lys	Ile	
					470					475					480	
	Trp	Asn	Gly	Met	Val	Gly	Glu	Leu	Val	Tyr	Gly	Lys	Ala	Asp	Ile	
30					485					490					495	
	Ala	Ile	Ala	Pro	Leu	Thr	Ile	Thr	Leu	Val	Arg	Glu	Glu	Val	Ile	
					500					505					510	
	Asp	Phe	Ser	Lys	Pro	Phe	Met	Ser	Leu	Gly	Ile	Ser	Ile	Met	Ile	
35					515					520					525	
	Lys	Lys	Pro	Gln	Lys	Ser	Lys	Pro	Gly	Val	Phe	Ser	Phe	Leu	Asp	
					530					535					540	
40	Pro	Leu	Ala	Tyr	Glu	Ile	Trp	Met	Cys	Ile	Val	Phe	Ala	Tyr	Ile	
					545					550					555	
	Gly	Val	Ser	Val	Val	Leu	Phe	Leu	Val	Ser	Arg	Phe	Ser	Pro	Tyr	
					560					565					570	
45	Glu	Trp	His	Thr	Glu	Glu	Phe	Glu	Asp	Gly	Arg	Glu	Thr	Gln	Ser	
					575					580					585	
	Ser	Glu	Ser	Thr	Asn	Glu	Phe	Gly	Ile	Phe	Asn	Ser	Leu	Trp	Phe	
					590					595					600	
50	Ser	Leu	Gly	Ala	Phe	Met	Arg	Gln	Gly	Cys	Asp	Ile	Ser	Pro	Arg	
					605					610					615	
	Ser	Leu	Ser	Gly	Arg	Ile	Val	Gly	Gly	Val	Trp	Trp	Phe	Phe	Thr	
					620					625					630	
55	Leu	Ile	Ile	Ile	Ser	Ser	Tyr	Thr	Ala	Asn	Leu	Ala	Ala	Phe	Leu	

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	635	640	645
5	Thr Val Glu Arg Met Val Ser Pro Ile Glu Ser Ala Glu Asp Leu 650	655	660
	Ser Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu Asp Ser Gly Ser 665	670	675
10	Thr Lys Glu Phe Phe Arg Arg Ser Lys Ile Ala Val Phe Asp Lys 680	685	690
	Met Trp Thr Tyr Met Arg Ser Ala Glu Pro Ser Val Phe Val Arg 695	700	705
15	Thr Thr Ala Glu Gly Val Ala Arg Val Arg Lys Ser Lys Gly Lys 710	715	720
	Tyr Ala Tyr Leu Leu Glu Ser Thr Met Asn Glu Tyr Ile Glu Gln 725	730	735
20	Arg Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser 740	745	750
	Lys Gly Tyr Gly Ile Ala Thr Pro Lys Gly Ser Ser Leu Gly Thr 755	760	765
25	Pro Val Asn Leu Ala Val Leu Lys Leu Ser Glu Gln Gly Val Leu 770	775	780
	Asp Lys Leu Lys Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly 785	790	795
30	Ala Lys Asp Ser Gly Ser Lys Glu Lys Thr Ser Ala Leu Ser Leu 800	805	810
	Ser Asn Val Ala Gly Val Phe Tyr Ile Leu Val Gly Gly Leu Gly 815	820	825
35	Leu Ala Met Leu Val Ala Leu Ile Glu Phe Cys Tyr Lys Ser Arg 830	835	840
	Ala Glu Ala Lys Arg Met Lys Val Ala Lys Asn Ala Gln Asn Ile 845	850	855
40	Asn Pro Ser Ser Ser Gln Asn Ser Gln Asn Phe Ala Thr Tyr Lys 860	865	870
	Glu Gly Tyr Asn Val Tyr Gly Ile Glu Ser Val Lys Ile 875	880	
45			
	<210> 142		
	<211> 357		
	<212> PRT		
	<213> Homo Sapien		
50			
	<400> 142		
	Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser 1	5	10
			15
55	Lys Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val 20	25	30

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5	Leu Glu Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe	35	40	45
	Met Leu Thr Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn	50	55	60
10	Arg Arg Lys Met Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val	65	70	75
	Leu Gly Ile Phe Gly Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp	80	85	90
15	Gly Ser Thr Gly Pro Thr Arg Phe Phe Leu Phe Gly Ile Leu Phe	95	100	105
	Ser Ile Cys Phe Ser Cys Leu Leu Ala His Ala Val Ser Leu Thr	110	115	120
20	Lys Leu Val Arg Gly Arg Lys Pro Leu Ser Leu Leu Val Ile Leu	125	130	135
	Gly Leu Ala Val Gly Phe Ser Leu Val Gln Asp Val Ile Ala Ile	140	145	150
25	Glu Tyr Ile Val Leu Thr Met Asn Arg Thr Asn Val Asn Val Phe	155	160	165
	Ser Glu Leu Ser Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu	170	175	180
30	Leu Thr Tyr Val Leu Phe Leu Met Ala Leu Thr Phe Leu Met Ser	185	190	195
	Ser Phe Thr Phe Cys Gly Ser Phe Thr Gly Trp Lys Arg His Gly	200	205	210
35	Ala His Ile Tyr Leu Thr Met Leu Leu Ser Ile Ala Ile Trp Val	215	220	225
	Ala Trp Ile Thr Leu Leu Met Leu Pro Asp Phe Asp Arg Arg Trp	230	235	240
40	Asp Asp Thr Ile Leu Ser Ser Ala Leu Ala Ala Asn Gly Trp Val	245	250	255
	Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe Trp Leu Leu Thr Lys	260	265	270
45	Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp Ala Phe Cys Lys	275	280	285
	Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn Arg Ala Tyr	290	295	300
50	Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly Asp Thr	305	310	315
	Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln Pro	320	325	330
55				

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Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser
335 340 345

5 Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser
350 355

<210> 143
<211> 222
<212> PRT
10 <213> Homo Sapien

<400> 143
Met Leu Pro Ala Gln Glu Ala Ala Lys Leu Tyr His Thr Asn Tyr
1 5 10 15

15 Val Arg Asn Ser Arg Ala Ile Gly Val Leu Trp Ala Ile Phe Thr
20 25 30

Ile Cys Phe Ala Ile Val Asn Val Val Cys Phe Ile Gln Pro Tyr
35 40 45

20 Trp Ile Gly Asp Gly Val Asp Thr Pro Gln Ala Gly Tyr Phe Gly
50 55 60

Leu Phe His Tyr Cys Ile Gly Asn Gly Phe Ser Arg Glu Leu Thr
65 70 75

25 Cys Arg Gly Ser Phe Thr Asp Phe Ser Thr Leu Pro Ser Gly Ala
80 85 90

Phe Lys Ala Ala Ser Phe Phe Ile Gly Leu Ser Met Met Leu Ile
95 100 105

30 Ile Ala Cys Ile Ile Cys Phe Thr Leu Phe Phe Phe Cys Asn Thr
110 115 120

Ala Thr Val Tyr Lys Ile Cys Ala Trp Met Gln Leu Thr Ser Ala
125 130 135

35 Ala Cys Leu Val Leu Gly Cys Met Ile Phe Pro Asp Gly Trp Asp
140 145 150

Ser Asp Glu Val Lys Arg Met Cys Gly Glu Lys Thr Asp Lys Tyr
155 160 165

40 Thr Leu Gly Ala Cys Ser Val Arg Trp Ala Tyr Ile Leu Ala Ile
170 175 180

Ile Gly Ile Leu Asp Ala Leu Ile Leu Ser Phe Leu Ala Phe Val
185 190 195

Leu Gly Asn Arg Gln Asp Ser Leu Met Ala Glu Glu Leu Lys Ala
200 205 210

50 Glu Asn Lys Val Leu Leu Ser Gln Tyr Ser Leu Glu
215 220

<210> 144
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<212> PRT
55 <213> Homo Sapien

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<400> 144

5	Met	Pro	Gly	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Met	1	5	10	15
	Leu	Pro	Ala	Gln	Glu	Ala	Ala	Lys	Leu	Tyr	His	Thr	Asn	Tyr	Val	20	25	30	
10	Arg	Asn	Ser	Arg	Ala	Ile	Gly	Val	Leu	Trp	Ala	Ile	Phe	Thr	Ile	35	40	45	
	Cys	Phe	Ala	Ile	Val	Asn	Val	Val	Cys	Phe	Ile	Gln	Pro	Tyr	Trp	50	55	60	
15	Ile	Gly	Asp	Gly	Val	Asp	Thr	Pro	Gln	Ala	Gly	Tyr	Phe	Gly	Leu	65	70	75	
	Phe	His	Tyr	Cys	Ile	Gly	Asn	Gly	Phe	Ser	Arg	Glu	Leu	Thr	Cys	80	85	90	
20	Arg	Gly	Ser	Phe	Thr	Asp	Phe	Ser	Thr	Leu	Pro	Ser	Gly	Ala	Phe	95	100	105	
	Lys	Ala	Ala	Ser	Phe	Phe	Ile	Gly	Leu	Ser	Met	Met	Leu	Ile	Ile	110	115	120	
25	Ala	Cys	Ile	Ile	Cys	Phe	Thr	Leu	Phe	Phe	Phe	Cys	Asn	Thr	Ala	125	130	135	
	Thr	Val	Tyr	Lys	Ile	Cys	Ala	Trp	Met	Gln	Leu	Thr	Ser	Ala	Ala	140	145	150	
30	Cys	Leu	Val	Leu	Gly	Cys	Met	Ile	Phe	Pro	Asp	Gly	Trp	Asp	Ser	155	160	165	
	Asp	Glu	Val	Lys	Arg	Met	Cys	Gly	Glu	Lys	Thr	Asp	Lys	Tyr	Thr	170	175	180	
35	Leu	Gly	Ala	Cys	Ser	Val	Arg	Trp	Ala	Tyr	Ile	Leu	Ala	Ile	Ile	185	190	195	
	Gly	Ile	Leu	Asp	Ala	Leu	Ile	Leu	Ser	Phe	Leu	Ala	Phe	Val	Leu	200	205	210	
40	Gly	Asn	Arg	Gln	Asp	Ser	Leu	Met	Ala	Glu	Glu	Leu	Lys	Ala	Glu	215	220	225	
	Asn	Lys	Val	Leu	Leu	Ser	Gln	Tyr	Ser	Leu	Glu					230	235		

<210> 145

<211> 236

<212> PRT

<213> Homo Sapien

50

<400> 145

55	Met	Pro	Gly	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Met	1	5	10	15	
	Leu	Pro	Ala	Gln	Glu	Ala	Ala	Lys	Leu	Tyr	His	Thr	Asn	Tyr	Val	20	25	30	

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5	Arg Asn Ser Arg Ala Ile Gly Val Leu Trp Ala Ile Phe Thr Ile	35	40	45
	Cys Phe Ala Ile Val Asn Val Val Cys Phe Ile Gln Pro Tyr Trp	50	55	60
10	Ile Gly Asp Gly Val Asp Thr Pro Gln Ala Gly Tyr Phe Gly Leu	65	70	75
	Phe His Tyr Cys Ile Gly Asn Gly Phe Ser Arg Glu Leu Thr Cys	80	85	90
15	Arg Gly Ser Phe Thr Asp Phe Ser Thr Leu Pro Ser Gly Ala Phe	95	100	105
	Lys Ala Ala Ser Phe Phe Ile Gly Leu Ser Met Met Leu Ile Ile	110	115	120
20	Ala Cys Ile Ile Cys Phe Thr Leu Phe Phe Phe Cys Asn Thr Ala	125	130	135
	Thr Val Tyr Lys Ile Cys Ala Trp Met Gln Leu Thr Ser Ala Ala	140	145	150
25	Cys Leu Val Leu Gly Cys Met Ile Phe Pro Asp Gly Trp Asp Ser	155	160	165
	Asp Glu Val Lys Arg Met Cys Gly Glu Lys Thr Asp Lys Tyr Thr	170	175	180
30	Leu Gly Ala Cys Ser Val Arg Trp Ala Tyr Ile Leu Ala Ile Ile	185	190	195
	Gly Ile Leu Asp Ala Leu Ile Leu Ser Phe Leu Ala Phe Val Leu	200	205	210
35	Gly Asn Arg Gln Asp Ser Leu Met Ala Glu Glu Leu Lys Ala Glu	215	220	225
	Asn Lys Val Leu Leu Ser Gln Tyr Ser Leu Glu	230	235	
40	<210> 146 <211> 408 <212> PRT <213> Homo Sapien			
45	<400> 146			
	Arg Pro Leu Arg Leu Pro Cys Arg Gly Pro Arg Ala Ala Gly Thr	1	5	10
	Val Ser Ser Glu Ser Leu Gly His Pro Ala Pro Gly Gln Val Thr	20	25	30
50	Asn Arg Ser Pro Gln Phe Pro Met Glu Leu Phe Gln Ser Ser Pro	35	40	45
	Arg Pro Pro Leu Gln Pro Val Cys Val Cys Pro Gly Leu Glu Leu	50	55	60
55				

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	Cys Asp Pro Pro His Arg Leu Ala Phe Ser Met Gly Ala Gly Leu	65	70	75
5	Phe Ser Val Val Gly Thr Leu Leu Leu Pro Gly Leu Ala Ala Leu	80	85	90
	Val Gln Asp Trp Arg Leu Leu Gln Gly Leu Gly Ala Leu Met Ser	95	100	105
10	Gly Leu Leu Leu Leu Phe Trp Gly Phe Pro Ala Leu Phe Pro Glu	110	115	120
	Ser Pro Cys Trp Leu Leu Ala Thr Gly Gln Val Ala Arg Ala Arg	125	130	135
15	Lys Ile Leu Trp Arg Phe Ala Glu Ala Ser Gly Val Gly Pro Gly	140	145	150
	Asp Ser Ser Leu Glu Glu Asn Ser Leu Ala Thr Glu Leu Thr Met	155	160	165
20	Leu Ser Ala Arg Ser Pro Gln Pro Arg Tyr His Ser Pro Leu Gly	170	175	180
	Leu Leu Arg Thr Arg Val Thr Trp Arg Asn Gly Leu Ile Leu Gly	185	190	195
25	Phe Ser Ser Leu Val Gly Gly Gly Ile Arg Ala Ser Phe Arg Arg	200	205	210
	Ser Leu Ala Pro Gln Val Pro Thr Phe Tyr Leu Pro Tyr Phe Leu	215	220	225
30	Glu Ala Gly Leu Glu Ala Ala Ala Leu Val Phe Leu Leu Leu Thr	230	235	240
	Ala Asp Cys Cys Gly Arg Arg Pro Val Leu Leu Leu Gly Thr Met	245	250	255
35	Val Thr Gly Leu Ala Ser Leu Leu Leu Leu Ala Gly Ala Gln Tyr	260	265	270
	Leu Pro Gly Trp Thr Val Leu Phe Leu Ser Val Leu Gly Leu Leu	275	280	285
40	Ala Ser Arg Ala Val Ser Ala Leu Ser Ser Leu Phe Ala Ala Glu	290	295	300
45	Val Phe Pro Thr Val Ile Arg Gly Ala Gly Leu Gly Leu Val Leu	305	310	315
	Gly Ala Gly Phe Leu Gly Gln Ala Ala Gly Pro Leu Asp Thr Leu	320	325	330
50	His Gly Arg Gln Gly Phe Phe Leu Gln Gln Val Val Phe Ala Ser	335	340	345
	Leu Ala Val Leu Ala Leu Leu Cys Val Leu Leu Leu Pro Glu Ser	350	355	360
55	Arg Ser Arg Gly Leu Pro Gln Ser Leu Gln Asp Ala Asp Arg Leu			

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		365		370		375
5	Arg Arg Ser Pro	Leu Leu Arg Gly Arg	Pro Arg Gln Asp His	Leu		
		380	385		390	
	Pro Leu Leu Pro	Pro Ser Asn Ser Tyr	Trp Ala Gly His Thr	Pro		
		395	400	405		
10	Glu Gln His					
	<210> 147					
	<211> 1152					
	<212> PRT					
15	<213> Homo Sapien					
	<220>					
	<221> unsure					
	<222> 382					
20	<223> unknown amino acid					
	<400> 147					
	Met Pro Phe Glu Gln Cys His Leu Ser	Trp Lys Asn Val Arg Arg				
	1	5	10	15		
25	Leu Tyr Asn Ala Val Ser Lys Glu Leu	Val Gly Glu Phe Leu Gln				
		20	25	30		
	Phe Val Gln Leu Asp Lys Glu Ala Ser	Asp Pro Phe Ser Leu Asn				
		35	40	45		
30	Glu Leu Leu Asp Glu Leu Ser Arg Lys	Gln Lys Glu Glu Leu Trp				
		50	55	60		
	Gln Arg Leu Lys Asn Leu Leu Thr Asp	Val Leu Leu Glu Ser Pro				
		65	70	75		
35	Val Asp Gly Trp Gln Val Val Glu Ala	Gln Gly Glu Asp Asn Met				
		80	85	90		
	Glu Thr Glu His Gly Ser Lys Met Arg	Lys Ser Ile Glu Ile Ile				
		95	100	105		
40	Tyr Ala Ile Thr Ser Val Ile Leu Ala	Ser Val Ser Val Ile Asn				
		110	115	120		
	Glu Ser Glu Asn Tyr Glu Ala Leu Leu	Glu Cys Val Ile Ile Leu				
		125	130	135		
45	Asn Gly Ile Leu Tyr Ala Leu Pro Glu	Ser Glu Arg Lys Leu Gln				
		140	145	150		
	Ser Ser Ile Gln Asp Leu Cys Val Thr	Trp Trp Glu Lys Gly Leu				
		155	160	165		
50	Pro Ala Lys Glu Asp Thr Gly Lys Thr	Ala Phe Val Met Leu Leu				
		170	175	180		
	Arg Arg Ser Leu Glu Thr Lys Thr Gly	Ala Asp Val Cys Arg Leu				
55		185	190	195		

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	Trp	Arg	Ile	His	Gln	Ala	Leu	Tyr	Cys	Phe	Asp	Tyr	Asp	Leu	Glu
					200					205					210
5	Glu	Ser	Gly	Glu	Ile	Lys	Asp	Met	Leu	Leu	Glu	Cys	Phe	Ile	Asn
					215					220					225
	Ile	Asn	Tyr	Ile	Lys	Lys	Glu	Glu	Gly	Arg	Arg	Phe	Leu	Ser	Cys
					230					235					240
10	Leu	Phe	Asn	Trp	Asn	Ile	Asn	Phe	Ile	Lys	Met	Ile	His	Gly	Thr
					245					250					255
	Ile	Lys	Asn	Gln	Leu	Gln	Gly	Leu	Gln	Lys	Ser	Leu	Met	Val	Tyr
					260					265					270
15	Ile	Ala	Glu	Ile	Tyr	Phe	Arg	Ala	Trp	Lys	Lys	Ala	Ser	Gly	Lys
					275					280					285
	Ile	Leu	Glu	Ala	Ile	Glu	Asn	Asp	Cys	Ile	Gln	Asp	Phe	Met	Phe
					290					295					300
20	His	Gly	Ile	His	Leu	Pro	Arg	Arg	Ser	Pro	Val	His	Ser	Lys	Val
					305					310					315
	Arg	Glu	Val	Leu	Ser	Tyr	Phe	His	His	Gln	Lys	Lys	Val	Arg	Gln
25					320					325					330
	Gly	Val	Glu	Glu	Met	Leu	Tyr	Arg	Leu	Tyr	Lys	Pro	Ile	Leu	Trp
					335					340					345
	Arg	Gly	Leu	Lys	Ala	Arg	Asn	Ser	Glu	Val	Arg	Ser	Asn	Ala	Ala
30					350					355					360
	Leu	Leu	Phe	Val	Glu	Ala	Phe	Pro	Ile	Arg	Asp	Pro	Asn	Leu	His
					365					370					375
	Ala	Ile	Glu	Met	Asp	Ser	Xaa	Ile	Gln	Lys	Gln	Phe	Glu	Glu	Leu
35					380					385					390
	Tyr	Ser	Leu	Leu	Glu	Asp	Pro	Tyr	Pro	Met	Val	Arg	Ser	Thr	Gly
					395					400					405
40	Ile	Leu	Gly	Val	Cys	Lys	Ile	Thr	Ser	Lys	Tyr	Trp	Glu	Met	Met
					410					415					420
	Pro	Pro	Thr	Ile	Leu	Ile	Asp	Leu	Leu	Lys	Lys	Val	Thr	Gly	Glu
					425					430					435
45	Leu	Ala	Phe	Asp	Thr	Ser	Ser	Ala	Asp	Val	Arg	Cys	Ser	Val	Phe
					440					445					450
	Lys	Cys	Leu	Pro	Met	Ile	Leu	Asp	Asn	Lys	Leu	Ser	His	Pro	Leu
					455					460					465
50	Leu	Glu	Gln	Leu	Leu	Pro	Ala	Leu	Arg	Tyr	Ser	Leu	His	Asp	Asn
					470					475					480
	Ser	Glu	Lys	Val	Arg	Val	Ala	Phe	Val	Asp	Met	Leu	Leu	Lys	Ile
					485					490					495
55	Lys	Ala	Val	Arg	Ala	Ala	Lys	Phe	Trp	Lys	Ile	Cys	Pro	Met	Glu

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	500	505	510
5	His Ile Leu Val Arg Leu Glu Thr Asp Ser Arg Pro Val Ser Arg 515 520 525		
	Arg Leu Val Ser Leu Ile Phe Asn Ser Phe Leu Pro Val Asn Gln 530 535 540		
10	Pro Glu Glu Val Trp Cys Glu Arg Cys Val Thr Leu Val Gln Met 545 550 555		
	Asn His Ala Ala Ala Arg Arg Phe Tyr Gln Tyr Ala His Glu His 560 565 570		
15	Thr Ala Cys Thr Asn Ile Ala Lys Leu Ile His Val Ile Arg His 575 580 585		
	Cys Leu Asn Ala Cys Ile Gln Arg Ala Val Arg Glu Pro Pro Glu 590 595 600		
20	Asp Glu Glu Glu Glu Asp Gly Arg Glu Lys Glu Asn Val Thr Val 605 610 615		
	Leu Asp Lys Thr Leu Ser Val Asn Asp Val Ala Cys Met Ala Gly 620 625 630		
25	Leu Leu Glu Ile Ile Val Ile Leu Trp Lys Ser Ile Asp Arg Ser 635 640 645		
	Met Glu Asn Asn Lys Glu Ala Lys Leu Tyr Thr Ile Asn Lys Phe 650 655 660		
30	Ala Ser Val Leu Pro Glu Tyr Leu Lys Val Phe Lys Asp Asp Arg 665 670 675		
	Cys Lys Ile Pro Leu Phe Met Leu Met Ser Phe Met Pro Ala Ser 680 685 690		
35	Ala Val Pro Pro Phe Ser Cys Gly Val Ile Ser Thr Leu Arg Ser 695 700 705		
	Arg Glu Glu Gly Ala Val Asp Lys Ser Tyr Cys Thr Leu Leu Asp 710 715 720		
40	Cys Leu Cys Ser Trp Gly Gln Val Gly His Ile Leu Glu Leu Val 725 730 735		
	Asp Asn Trp Leu Pro Thr Glu His Ala Gln Ala Lys Ser Asn Thr 740 745 750		
45	Ala Ser Lys Gly Arg Val Gln Ile His Asp Thr Arg Pro Val Lys 755 760 765		
	Pro Glu Leu Ala Leu Val Tyr Ile Glu Tyr Leu Leu Thr His Pro 770 775 780		
50	Lys Asn Arg Glu Cys Leu Leu Ser Ala Pro Arg Lys Lys Leu Asn 785 790 795		
	His Leu Leu Lys Ala Leu Glu Thr Ser Lys Ala Asp Leu Glu Ser 800 805 810		
55			

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5	Leu Leu Gln Thr	Pro Gly Gly Lys Pro	Arg Gly Phe Ser Glu Ala	815	820	825
	Ala Ala Pro Arg	Ala Phe Gly Leu His	Cys Arg Leu Ser Ile His	830	835	840
10	Leu Gln His Lys	Phe Cys Ser Glu Gly	Lys Val Tyr Leu Ser Met	845	850	855
	Leu Glu Asp Thr	Gly Phe Trp Leu Glu	Ser Lys Ile Leu Ser Phe	860	865	870
15	Ile Gln Asp Gln	Glu Glu Asp Tyr Leu	Lys Leu His Arg Val Ile	875	880	885
	Tyr Gln Gln Ile	Ile Gln Thr Tyr Leu	Thr Val Cys Lys Asp Val	890	895	900
20	Val Met Val Gly	Leu Gly Asp His Gln	Phe Gln Met Gln Leu Leu	905	910	915
	Gln Arg Ser Leu	Gly Ile Met Gln Thr	Val Lys Gly Phe Phe Tyr	920	925	930
25	Val Ser Leu Leu	Leu Asp Ile Leu Lys	Glu Ile Thr Gly Ser Ser	935	940	945
	Leu Ile Gln Lys	Thr Asp Ser Asp Glu	Glu Val Ala Met Leu Leu	950	955	960
30	Asp Thr Val Gln	Lys Val Phe Gln Lys	Met Leu Glu Cys Ile Ala	965	970	975
	Arg Ser Phe Arg	Lys Gln Pro Glu Glu	Gly Leu Arg Leu Leu Tyr	980	985	990
35	Ser Val Gln Arg	Pro Leu His Glu Phe	Ile Thr Ala Val Gln Ser	995	1000	1005
	Arg His Thr Asp	Thr Pro Val His Arg	Gly Val Leu Ser Thr Leu	1010	1015	1020
40	Ile Ala Gly Pro	Val Val Glu Ile Ser	His Gln Leu Arg Lys Val	1025	1030	1035
	Ser Asp Val Glu	Glu Leu Thr Pro Pro	Glu His Leu Ser Asp Leu	1040	1045	1050
45	Pro Pro Phe Ser	Arg Cys Leu Ile Gly	Ile Ile Ile Lys Ser Ser	1055	1060	1065
	Asn Val Val Arg	Ser Phe Leu Asp Glu	Leu Lys Ala Cys Val Ala	1070	1075	1080
50	Ser Asn Asp Ile	Glu Gly Ile Val Cys	Leu Thr Ala Ala Val His	1085	1090	1095
55	Ile Ile Leu Val	Ile Asn Ala Gly Lys	His Lys Ser Ser Lys Val	1100	1105	1110

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	Arg Glu Val Ala Ala Thr Val His Arg Lys Leu Lys Thr Phe Met	
	1115	1120 1125
5	Glu Ile Thr Leu Glu Glu Asp Ser Ile Glu Arg Phe Leu Tyr Glu	
	1130	1135 1140
	Ser Ser Ser Arg Thr Leu Gly Glu Leu Leu Asn Ser	
	1145	1150
10	<210> 148	
	<211> 1143	
	<212> PRT	
	<213> Homo Sapien	
15	<400> 148	
	Met Glu Lys Arg Glu Thr Phe Val Gln Ala Val Ser Lys Glu Leu	
	1	5 10 15
	Val Gly Glu Phe Leu Gln Phe Val Gln Leu Asp Lys Glu Ala Ser	
	20	25 30
20	Asp Pro Phe Ser Leu Asn Glu Leu Leu Asp Glu Leu Ser Arg Lys	
	35	40 45
	Gln Lys Glu Glu Leu Trp Gln Arg Leu Lys Asn Leu Leu Thr Asp	
	50	55 60
25	Val Leu Leu Glu Ser Pro Val Asp Gly Trp Gln Val Val Glu Ala	
	65	70 75
	Gln Gly Glu Asp Asn Met Glu Thr Glu His Gly Ser Lys Met Arg	
	80	85 90
30	Lys Ser Ile Glu Ile Ile Tyr Ala Ile Thr Ser Val Ile Leu Ala	
	95	100 105
	Ser Val Ser Val Ile Asn Glu Ser Glu Asn Tyr Glu Ala Leu Leu	
	110	115 120
35	Glu Cys Val Ile Ile Leu Asn Gly Ile Leu Tyr Ala Leu Pro Glu	
	125	130 135
	Ser Glu Arg Lys Leu Gln Ser Ser Ile Gln Asp Leu Cys Val Thr	
	140	145 150
40	Trp Trp Glu Lys Gly Leu Pro Ala Lys Glu Asp Thr Gly Lys Thr	
	155	160 165
45	Ala Phe Val Met Leu Leu Arg Arg Ser Leu Glu Thr Lys Thr Gly	
	170	175 180
	Ala Asp Val Cys Arg Leu Trp Arg Ile His Gln Ala Leu Tyr Cys	
	185	190 195
50	Phe Asp Tyr Asp Leu Glu Glu Ser Gly Glu Ile Lys Asp Met Leu	
	200	205 210
	Leu Glu Cys Phe Ile Asn Ile Asn Tyr Ile Lys Lys Glu Glu Gly	
	215	220 225
55	Arg Arg Phe Leu Ser Cys Leu Phe Asn Trp Asn Ile Asn Phe Ile	

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					230					235					240
5	Lys	Met	Ile	His	Gly	Thr	Ile	Lys	Asn	Gln	Leu	Gln	Gly	Leu	Gln
					245					250					255
	Lys	Ser	Leu	Met	Val	Tyr	Ile	Ala	Glu	Ile	Tyr	Phe	Arg	Ala	Trp
					260					265					270
10	Lys	Lys	Ala	Ser	Gly	Lys	Ile	Leu	Glu	Ala	Ile	Glu	Asn	Asp	Cys
					275					280					285
	Ile	Gln	Asp	Phe	Met	Phe	His	Gly	Ile	His	Leu	Pro	Arg	Arg	Ser
					290					295					300
15	Pro	Val	His	Ser	Lys	Val	Arg	Glu	Val	Leu	Ser	Tyr	Phe	His	His
					305					310					315
	Gln	Lys	Lys	Val	Arg	Gln	Gly	Val	Glu	Glu	Met	Leu	Tyr	Arg	Leu
					320					325					330
20	Tyr	Lys	Pro	Ile	Leu	Trp	Arg	Gly	Leu	Lys	Ala	Arg	Asn	Ser	Glu
					335					340					345
	Val	Arg	Ser	Asn	Ala	Ala	Leu	Leu	Phe	Val	Glu	Ala	Phe	Pro	Ile
					350					355					360
25	Arg	Asp	Pro	Asn	Leu	His	Ala	Ile	Glu	Met	Asp	Ser	Glu	Ile	Gln
					365					370					375
	Lys	Gln	Phe	Glu	Glu	Leu	Tyr	Ser	Leu	Leu	Glu	Asp	Pro	Tyr	Pro
					380					385					390
30	Met	Val	Arg	Ser	Thr	Gly	Ile	Leu	Gly	Val	Cys	Lys	Ile	Thr	Ser
					395					400					405
	Lys	Tyr	Trp	Glu	Met	Met	Pro	Pro	Thr	Ile	Leu	Ile	Asp	Leu	Leu
					410					415					420
35	Lys	Lys	Val	Thr	Gly	Glu	Leu	Ala	Phe	Asp	Thr	Ser	Ser	Ala	Asp
					425					430					435
	Val	Arg	Cys	Ser	Val	Phe	Lys	Cys	Leu	Pro	Met	Ile	Leu	Asp	Asn
					440					445					450
40	Lys	Leu	Ser	His	Pro	Leu	Leu	Glu	Gln	Leu	Leu	Pro	Ala	Leu	Arg
					455					460					465
	Tyr	Ser	Leu	His	Asp	Asn	Ser	Glu	Lys	Val	Arg	Val	Ala	Phe	Val
					470					475					480
45	Asp	Met	Leu	Leu	Lys	Ile	Lys	Ala	Val	Arg	Ala	Ala	Lys	Phe	Trp
					485					490					495
	Lys	Ile	Cys	Pro	Met	Glu	His	Ile	Leu	Val	Arg	Leu	Glu	Thr	Asp
					500					505					510
	Ser	Arg	Pro	Val	Ser	Arg	Arg	Leu	Val	Ser	Leu	Ile	Phe	Asn	Ser
					515					520					525
55	Phe	Leu	Pro	Val	Asn	Gln	Pro	Glu	Glu	Val	Trp	Cys	Glu	Arg	Cys
					530					535					540

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5	Val Thr Leu Val	Gln Met Asn His Ala	Ala Ala Arg Arg Phe Tyr	545	550	555
	Gln Tyr Ala His	Glu His Thr Ala Cys	Thr Asn Ile Ala Lys Leu	560	565	570
10	Ile His Val Ile	Arg His Cys Leu Asn	Ala Cys Ile Gln Arg Ala	575	580	585
	Val Arg Glu Pro	Pro Glu Asp Glu Glu	Glu Glu Asp Gly Arg Glu	590	595	600
15	Lys Glu Asn Val	Thr Val Leu Asp Lys	Thr Leu Ser Val Asn Asp	605	610	615
	Val Ala Cys Met	Ala Gly Leu Leu Glu	Ile Ile Val Ile Leu Trp	620	625	630
20	Lys Ser Ile Asp	Arg Ser Met Glu Asn	Asn Lys Glu Ala Lys Leu	635	640	645
	Tyr Thr Ile Asn	Lys Phe Ala Ser Val	Leu Pro Glu Tyr Leu Lys	650	655	660
25	Val Phe Lys Asp	Asp Arg Cys Lys Ile	Pro Leu Phe Met Leu Met	665	670	675
	Ser Phe Met Pro	Ala Ser Ala Val Pro	Pro Phe Ser Cys Gly Val	680	685	690
30	Ile Ser Thr Leu	Arg Ser Arg Glu Glu	Gly Ala Val Asp Lys Ser	695	700	705
	Tyr Cys Thr Leu	Leu Asp Cys Leu Cys	Ser Trp Gly Gln Val Gly	710	715	720
35	His Ile Leu Glu	Leu Val Asp Asn Trp	Leu Pro Thr Glu His Ala	725	730	735
	Gln Ala Lys Ser	Asn Thr Ala Ser Lys	Gly Arg Val Gln Ile His	740	745	750
40	Asp Thr Arg Pro	Val Lys Pro Glu Leu	Ala Leu Val Tyr Ile Glu	755	760	765
	Tyr Leu Leu Thr	His Pro Lys Asn Arg	Glu Cys Leu Leu Ser Ala	770	775	780
45	Pro Arg Lys Lys	Leu Asn His Leu Leu	Lys Ala Leu Glu Thr Ser	785	790	795
	Lys Ala Asp Leu	Glu Ser Leu Leu Gln	Thr Pro Gly Gly Lys Pro	800	805	810
50	Arg Gly Phe Ser	Glu Ala Ala Ala Pro	Arg Ala Phe Gly Leu His	815	820	825
55	Cys Arg Leu Ser	Ile His Leu Gln His	Lys Phe Cys Ser Glu Gly	830	835	840

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	Lys Val Tyr Leu Ser Met Leu Glu Asp Thr Gly Phe Trp Leu Glu	845	850	855
5	Ser Lys Ile Leu Ser Phe Ile Gln Asp Gln Glu Glu Asp Tyr Leu	860	865	870
	Lys Leu His Arg Val Ile Tyr Gln Gln Ile Ile Gln Thr Tyr Leu	875	880	885
10	Thr Val Cys Lys Asp Val Val Met Val Gly Leu Gly Asp His Gln	890	895	900
	Phe Gln Met Gln Leu Leu Gln Arg Ser Leu Gly Ile Met Gln Thr	905	910	915
15	Val Lys Gly Phe Phe Tyr Val Ser Leu Leu Leu Asp Ile Leu Lys	920	925	930
	Glu Ile Thr Gly Ser Ser Leu Ile Gln Lys Thr Asp Ser Asp Glu	935	940	945
20	Glu Val Ala Met Leu Leu Asp Thr Val Gln Lys Val Phe Gln Lys	950	955	960
	Met Leu Glu Cys Ile Ala Arg Ser Phe Arg Lys Gln Pro Glu Glu	965	970	975
25	Gly Leu Arg Leu Leu Tyr Ser Val Gln Arg Pro Leu His Glu Phe	980	985	990
	Ile Thr Ala Val Gln Ser Arg His Thr Asp Thr Pro Val His Arg	995	1000	1005
30	Gly Val Leu Ser Thr Leu Ile Ala Gly Pro Val Val Glu Ile Ser	1010	1015	1020
	His Gln Leu Arg Lys Val Ser Asp Val Glu Glu Leu Thr Pro Pro	1025	1030	1035
35	Glu His Leu Ser Asp Leu Pro Pro Phe Ser Arg Cys Leu Ile Gly	1040	1045	1050
	Ile Ile Ile Lys Ser Ser Asn Val Val Arg Ser Phe Leu Asp Glu	1055	1060	1065
40	Leu Lys Ala Cys Val Ala Ser Asn Asp Ile Glu Gly Ile Val Cys	1070	1075	1080
	Leu Thr Ala Ala Val His Ile Ile Leu Val Ile Asn Ala Gly Lys	1085	1090	1095
45	His Lys Ser Ser Lys Val Arg Glu Val Ala Ala Thr Val His Arg	1100	1105	1110
50	Lys Leu Lys Thr Phe Met Glu Ile Thr Leu Glu Glu Asp Ser Ile	1115	1120	1125
	Glu Arg Phe Leu Tyr Glu Ser Ser Ser Arg Thr Leu Gly Glu Leu	1130	1135	1140
55	Leu Asn Ser			

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5 <210> 149
 <211> 384
 <212> PRT
 <213> Homo Sapien

 <400> 149
 10 Met Asn Ser Thr Leu Phe Ser Gln Val Glu Asn His Ser Val His
 1 5 10 15
 Ser Asn Phe Ser Glu Lys Asn Ala Gln Leu Leu Ala Phe Glu Asn
 20 25 30
 15 Asp Asp Cys His Leu Pro Leu Ala Met Ile Phe Thr Leu Ala Leu
 35 40 45
 Ala Tyr Gly Ala Val Ile Ile Leu Gly Val Ser Gly Asn Leu Ala
 50 55 60
 20 Leu Ile Ile Ile Ile Leu Lys Gln Lys Glu Met Arg Asn Val Thr
 65 70 75
 Asn Ile Leu Ile Val Asn Leu Ser Phe Ser Asp Leu Leu Val Ala
 80 85 90
 25 Ile Met Cys Leu Pro Phe Thr Phe Val Tyr Thr Leu Met Asp His
 95 100 105
 Trp Val Phe Gly Glu Ala Met Cys Lys Leu Asn Pro Phe Val Gln
 110 115 120
 30 Cys Val Ser Ile Thr Val Ser Ile Phe Ser Leu Val Leu Ile Ala
 125 130 135
 Val Glu Arg His Gln Leu Ile Ile Asn Pro Arg Gly Trp Arg Pro
 140 145 150
 35 Asn Asn Arg His Ala Tyr Val Gly Ile Ala Val Ile Trp Val Leu
 155 160 165
 Ala Val Ala Ser Ser Leu Pro Phe Leu Ile Tyr Gln Val Met Thr
 170 175 180
 40 Asp Glu Pro Phe Gln Asn Val Thr Leu Asp Ala Tyr Lys Asp Lys
 185 190 195
 Tyr Val Cys Phe Asp Gln Phe Pro Ser Asp Ser His Arg Leu Ser
 200 205 210
 45 Tyr Thr Thr Leu Leu Leu Val Leu Gln Tyr Phe Gly Pro Leu Cys
 215 220 225
 Phe Ile Phe Ile Cys Tyr Phe Lys Ile Tyr Ile Arg Leu Lys Arg
 230 235 240
 50 Arg Asn Asn Met Met Asp Lys Met Arg Asp Asn Lys Tyr Arg Ser
 245 250 255
 55 Ser Glu Thr Lys Arg Ile Asn Ile Met Leu Leu Ser Ile Val Val
 260 265 270

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5	Ala Phe Ala Val Cys Trp Leu Pro Leu Thr Ile Phe Asn Thr Val	275	280	285
	Phe Asp Trp Asn His Gln Ile Ile Ala Thr Cys Asn His Asn Leu	290	295	300
10	Leu Phe Leu Leu Cys His Leu Thr Ala Met Ile Ser Thr Cys Val	305	310	315
	Asn Pro Ile Phe Tyr Gly Phe Leu Asn Lys Asn Phe Gln Arg Asp	320	325	330
15	Leu Gln Phe Phe Phe Asn Phe Cys Asp Phe Arg Ser Arg Asp Asp	335	340	345
	Asp Tyr Glu Thr Ile Ala Met Ser Thr Met His Thr Asp Val Ser	350	355	360
20	Lys Thr Ser Leu Lys Gln Ala Ser Pro Val Ala Phe Lys Lys Ile	365	370	375
	Asn Asn Asn Asp Asp Asn Glu Lys Ile	380		
25	<210> 150			
	<211> 327			
	<212> PRT			
	<213> Homo Sapien			
30	<400> 150			
	Met Val Arg Cys Asp Arg Gly Leu Gln Met Leu Leu Thr Thr Ala	1	5	10
				15
	Gly Ala Phe Ala Ala Phe Ser Leu Met Ala Ile Ala Ile Gly Thr	20	25	30
35	Asp Tyr Trp Leu Tyr Ser Ser Ala His Ile Cys Asn Gly Thr Asn	35	40	45
	Leu Thr Met Asp Asp Gly Pro Pro Pro Arg Arg Ala Arg Gly Asp	50	55	60
40	Leu Thr His Ser Gly Leu Trp Arg Val Cys Cys Ile Glu Gly Ile	65	70	75
	Tyr Lys Gly His Cys Phe Arg Ile Asn His Phe Pro Glu Asp Asn	80	85	90
45	Asp Tyr Asp His Asp Ser Ser Glu Tyr Leu Leu Arg Ile Val Arg	95	100	105
	Ala Ser Ser Val Phe Pro Ile Leu Ser Thr Ile Leu Leu Leu Leu	110	115	120
50	Gly Gly Leu Cys Ile Gly Ala Gly Arg Ile Tyr Ser Arg Lys Asn	125	130	135
	Asn Ile Val Leu Ser Ala Gly Ile Leu Phe Val Ala Ala Gly Leu	140	145	150
55				

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	Ser Asn Ile Ile Gly Ile Ile Val Tyr Ile Ser Ser Asn Thr Gly	155	160	165
5	Asp Pro Ser Asp Lys Arg Asp Glu Asp Lys Lys Asn His Tyr Asn	170	175	180
	Tyr Gly Trp Ser Phe Tyr Phe Gly Ala Leu Ser Phe Ile Val Ala	185	190	195
10	Glu Thr Val Gly Val Leu Ala Val Asn Ile Tyr Ile Glu Lys Asn	200	205	210
	Lys Glu Leu Arg Phe Lys Thr Lys Arg Glu Phe Leu Lys Ala Ser	215	220	225
15	Ser Ser Ser Pro Tyr Ala Arg Met Pro Ser Tyr Arg Tyr Arg Arg	230	235	240
	Arg Arg Ser Arg Ser Ser Ser Arg Ser Thr Glu Ala Ser Pro Ser	245	250	255
20	Arg Asp Val Ser Pro Met Gly Leu Lys Ile Thr Gly Ala Ile Pro	260	265	270
	Met Gly Glu Leu Ser Met Tyr Thr Leu Ser Arg Glu Pro Leu Lys	275	280	285
25	Val Thr Thr Ala Ala Ser Tyr Ser Pro Asp Gln Glu Ala Ser Phe	290	295	300
	Leu Gln Val His Asp Phe Phe Gln Gln Asp Leu Lys Glu Gly Phe	305	310	315
30	His Val Ser Met Leu Asn Arg Arg Thr Thr Pro Val	320	325	
	<210> 151			
35	<211> 323			
	<212> PRT			
	<213> Homo Sapien			
	<400> 151			
40	Met Ala Arg Gly Pro Gly Leu Ala Pro Pro Pro Leu Arg Leu Pro	1	5	10 15
	Leu Leu Leu Leu Val Leu Ala Ala Val Thr Gly His Thr Ala Ala	20	25	30
45	Gln Asp Asn Cys Thr Cys Pro Thr Asn Lys Met Thr Val Cys Ser	35	40	45
	Pro Asp Gly Pro Gly Gly Arg Cys Gln Cys Arg Ala Leu Gly Ser	50	55	60
50	Gly Met Ala Val Asp Cys Ser Thr Leu Thr Ser Lys Cys Leu Leu	65	70	75
	Leu Lys Ala Arg Met Ser Ala Pro Lys Asn Ala Arg Thr Leu Val	80	85	90
55	Arg Pro Ser Glu His Ala Leu Val Asp Asn Asp Gly Leu Tyr Asp			

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				95					100					105	
5	Pro	Asp	Cys	Asp	Pro	Glu	Gly	Arg	Phe	Lys	Ala	Arg	Gln	Cys	Asn
				110						115				120	
	Gln	Thr	Ser	Val	Cys	Trp	Cys	Val	Asn	Ser	Val	Gly	Val	Arg	Arg
				125						130				135	
10	Thr	Asp	Lys	Gly	Asp	Leu	Ser	Leu	Arg	Cys	Asp	Glu	Leu	Val	Arg
				140						145				150	
	Thr	His	His	Ile	Leu	Ile	Asp	Leu	Arg	His	Arg	Pro	Thr	Ala	Gly
				155						160				165	
15	Ala	Phe	Asn	His	Ser	Asp	Leu	Asp	Ala	Glu	Leu	Arg	Arg	Leu	Phe
				170						175				180	
	Arg	Glu	Arg	Tyr	Arg	Leu	His	Pro	Lys	Phe	Val	Ala	Ala	Val	His
				185						190				195	
20	Tyr	Glu	Gln	Pro	Thr	Ile	Gln	Ile	Glu	Leu	Arg	Gln	Asn	Thr	Ser
				200						205				210	
	Gln	Lys	Ala	Ala	Gly	Glu	Val	Asp	Ile	Gly	Asp	Ala	Ala	Tyr	Tyr
				215						220				225	
25	Phe	Glu	Arg	Asp	Ile	Lys	Gly	Glu	Ser	Leu	Phe	Gln	Gly	Arg	Gly
				230						235				240	
	Gly	Leu	Asp	Leu	Arg	Val	Arg	Gly	Glu	Pro	Leu	Gln	Val	Glu	Arg
				245						250				255	
30	Thr	Leu	Ile	Tyr	Tyr	Leu	Asp	Glu	Ile	Pro	Pro	Lys	Phe	Ser	Met
				260						265				270	
	Lys	Arg	Leu	Thr	Ala	Gly	Leu	Ile	Ala	Val	Ile	Val	Val	Val	Val
				275						280				285	
35	Val	Ala	Leu	Val	Ala	Gly	Met	Ala	Val	Leu	Val	Ile	Thr	Asn	Arg
				290						295				300	
	Arg	Lys	Ser	Gly	Lys	Tyr	Lys	Lys	Val	Glu	Ile	Lys	Glu	Leu	Gly
				305						310				315	
40	Glu	Leu	Arg	Lys	Glu	Pro	Ser	Leu							
				320											
45	<210>	152													
	<211>	207													
	<212>	PRT													
	<213>	Homo Sapien													
50	<400>	152													
	Met	Gly	Lys	Cys	Ser	Gly	Arg	Cys	Thr	Leu	Val	Ala	Phe	Cys	Cys
	1				5					10				15	
	Leu	Gln	Leu	Val	Ala	Ala	Leu	Glu	Arg	Gln	Ile	Phe	Asp	Phe	Leu
				20						25				30	
55	Gly	Tyr	Gln	Trp	Ala	Pro	Ile	Leu	Ala	Asn	Phe	Leu	His	Ile	Met
				35						40				45	

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5	Ala Val Ile Leu Gly Ile Phe Gly Thr Val Gln Tyr Arg Ser Arg	50	55	60
	Tyr Leu Ile Leu Tyr Ala Ala Trp Leu Val Leu Trp Val Gly Trp	65	70	75
10	Asn Ala Phe Ile Ile Cys Phe Tyr Leu Glu Val Gly Gln Leu Ser	80	85	90
	Gln Asp Arg Asp Phe Ile Met Thr Phe Asn Thr Ser Leu His Arg	95	100	105
15	Ser Trp Trp Met Glu Asn Gly Pro Gly Cys Leu Val Thr Pro Val	110	115	120
	Leu Asn Ser Arg Leu Ala Leu Glu Asp His His Val Ile Ser Val	125	130	135
20	Thr Gly Cys Leu Leu Asp Tyr Pro Tyr Ile Glu Ala Leu Ser Ser	140	145	150
	Ala Leu Gln Ile Phe Leu Ala Leu Phe Gly Phe Val Phe Ala Cys	155	160	165
25	Tyr Val Ser Lys Val Phe Leu Glu Glu Glu Asp Ser Phe Asp Phe	170	175	180
	Ile Gly Gly Phe Asp Ser Tyr Gly Tyr Gln Ala Pro Gln Lys Thr	185	190	195
30	Ser His Leu Gln Leu Gln Pro Leu Tyr Thr Ser Gly	200	205	
35	<210> 153 <211> 581 <212> PRT <213> Homo Sapien			
	<400> 153			
40	Met Pro Ala Pro Arg Ala Arg Glu Gln Pro Arg Val Pro Gly Glu	1	5	10
	Arg Gln Pro Leu Leu Pro Arg Gly Ala Arg Gly Pro Arg Arg Trp	20	25	30
45	Arg Arg Ala Ala Gly Ala Ala Val Leu Leu Val Glu Met Leu Glu	35	40	45
	Arg Ala Ala Phe Phe Gly Val Thr Ala Asn Leu Val Leu Tyr Leu	50	55	60
50	Asn Ser Thr Asn Phe Asn Trp Thr Gly Glu Gln Ala Thr Arg Ala	65	70	75
	Ala Leu Val Phe Leu Gly Ala Ser Tyr Leu Leu Ala Pro Val Gly	80	85	90
55	Gly Trp Leu Ala Asp Val Tyr Leu Gly Arg Tyr Arg Ala Val Ala	95	100	105

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	Leu	Ser	Leu	Leu	Leu	Tyr	Leu	Ala	Ala	Ser	Gly	Leu	Leu	Pro	Ala	
					110					115					120	
5	Thr	Ala	Phe	Pro	Asp	Gly	Arg	Ser	Ser	Phe	Cys	Gly	Glu	Met	Pro	
					125					130					135	
	Ala	Ser	Pro	Leu	Gly	Pro	Ala	Cys	Pro	Ser	Ala	Gly	Cys	Pro	Arg	
					140					145					150	
10	Ser	Ser	Pro	Ser	Pro	Tyr	Cys	Ala	Pro	Val	Leu	Tyr	Ala	Gly	Leu	
					155					160					165	
	Leu	Leu	Leu	Gly	Leu	Ala	Ala	Ser	Ser	Val	Arg	Ser	Asn	Leu	Thr	
					170					175					180	
15	Ser	Phe	Gly	Ala	Asp	Gln	Val	Met	Asp	Leu	Gly	Arg	Asp	Ala	Thr	
					185					190					195	
	Arg	Arg	Phe	Phe	Asn	Trp	Phe	Tyr	Trp	Ser	Ile	Asn	Leu	Gly	Ala	
					200					205					210	
20	Val	Leu	Ser	Leu	Leu	Val	Val	Ala	Phe	Ile	Gln	Gln	Asn	Ile	Ser	
					215					220					225	
	Phe	Leu	Leu	Gly	Tyr	Ser	Ile	Pro	Val	Gly	Cys	Val	Gly	Leu	Ala	
25					230					235					240	
	Phe	Phe	Ile	Phe	Leu	Phe	Ala	Thr	Pro	Val	Phe	Ile	Thr	Lys	Pro	
					245					250					255	
	Pro	Met	Gly	Ser	Gln	Val	Ser	Ser	Met	Leu	Lys	Leu	Ala	Leu	Gln	
30					260					265					270	
	Asn	Cys	Cys	Pro	Gln	Leu	Trp	Gln	Arg	His	Ser	Ala	Arg	Asp	Arg	
					275					280					285	
	Gln	Cys	Ala	Arg	Val	Leu	Ala	Asp	Glu	Arg	Ser	Pro	Gln	Pro	Gly	
35					290					295					300	
	Ala	Ser	Pro	Gln	Glu	Asp	Ile	Ala	Asn	Phe	Gln	Val	Leu	Val	Lys	
					305					310					315	
	Ile	Leu	Pro	Val	Met	Val	Thr	Leu	Val	Pro	Tyr	Trp	Met	Val	Tyr	
40					320					325					330	
	Phe	Gln	Met	Gln	Ser	Thr	Tyr	Val	Leu	Gln	Gly	Leu	His	Leu	His	
					335					340					345	
45	Ile	Pro	Asn	Ile	Phe	Pro	Ala	Asn	Pro	Ala	Asn	Ile	Ser	Val	Ala	
					350					355					360	
	Leu	Arg	Ala	Gln	Gly	Ser	Ser	Tyr	Thr	Ile	Pro	Glu	Ala	Trp	Leu	
					365					370					375	
50	Leu	Leu	Ala	Asn	Val	Val	Val	Val	Leu	Ile	Leu	Val	Pro	Leu	Lys	
					380					385					390	
	Asp	Arg	Leu	Ile	Asp	Pro	Leu	Leu	Leu	Arg	Cys	Lys	Leu	Leu	Pro	
					395					400					405	
55	Ser	Ala	Leu	Gln	Lys	Met	Ala	Leu	Gly	Met	Phe	Phe	Gly	Phe	Thr	

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		410		415		420
5	Ser Val Ile Val	Ala Gly Val Leu Glu	Met Glu Arg Leu His Tyr			
		425	430		435	
	Ile His His Asn	Glu Thr Val Ser Gln	Gln Ile Gly Glu Val Leu			
		440	445		450	
10	Tyr Asn Ala Ala	Pro Leu Ser Ile Trp	Trp Gln Ile Pro Gln Tyr			
		455	460		465	
	Leu Leu Ile Gly	Ile Ser Glu Ile Phe	Ala Ser Ile Pro Gly Leu			
		470	475		480	
15	Glu Phe Ala Tyr	Ser Glu Ala Pro Arg	Ser Met Gln Gly Ala Ile			
		485	490		495	
	Met Gly Ile Phe	Phe Cys Leu Ser Gly	Val Gly Ser Leu Leu Gly			
		500	505		510	
20	Ser Ser Leu Val	Ala Leu Leu Ser Leu	Pro Gly Gly Trp Leu His			
		515	520		525	
	Cys Pro Lys Asp	Phe Gly Asn Ile Asn	Asn Cys Arg Met Asp Leu			
		530	535		540	
25	Tyr Phe Phe Leu	Leu Ala Gly Ile Gln	Ala Val Thr Ala Leu Leu			
		545	550		555	
	Phe Val Trp Ile	Ala Gly Arg Tyr Glu	Arg Ala Ser Gln Gly Pro			
		560	565		570	
30	Ala Ser His Ser	Arg Phe Ser Arg Asp	Arg Gly			
		575	580			
	<210> 154					
	<211> 1266					
35	<212> PRT					
	<213> Homo Sapien					
	<400> 154					
40	Met Trp Val Asn	Pro Glu Glu Val Leu Leu	Ala Asn Ala Leu Trp			
	1	5	10		15	
	Ile Thr Glu Arg	Ala Asn Pro Tyr Phe	Ile Leu Gln Arg Arg Lys			
		20	25		30	
45	Gly His Ala Gly	Asp Gly Gly Gly Gly	Gly Gly Leu Ala Gly Leu			
		35	40		45	
	Leu Val Gly Thr	Leu Asp Val Val Leu	Asp Ser Ser Ala Arg Val			
		50	55		60	
50	Ala Pro Tyr Arg	Ile Leu Tyr Gln Thr	Pro Asp Ser Leu Val Tyr			
		65	70		75	
	Trp Thr Ile Ala	Cys Gly Gly Ser Arg	Lys Glu Ile Thr Glu His			
		80	85		90	
55	Trp Glu Trp Leu	Glu Gln Asn Leu Leu	Gln Thr Leu Ser Ile Phe			
		95	100		105	

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	Glu Asn Glu Asn Asp Ile Thr Thr Phe Val Arg Gly Lys Ile Gln	110	115	120
5	Gly Ile Ile Ala Glu Tyr Asn Lys Ile Asn Asp Val Lys Glu Asp	125	130	135
	Asp Asp Thr Glu Lys Phe Lys Glu Ala Ile Val Lys Phe His Arg	140	145	150
10	Leu Phe Gly Met Pro Glu Glu Glu Lys Leu Val Asn Tyr Tyr Ser	155	160	165
	Cys Ser Tyr Trp Lys Gly Lys Val Pro Arg Gln Gly Trp Met Tyr	170	175	180
15	Leu Ser Ile Asn His Leu Cys Phe Tyr Ser Phe Leu Met Gly Arg	185	190	195
	Glu Ala Lys Leu Val Ile Arg Trp Val Asp Ile Thr Gln Leu Glu	200	205	210
20	Lys Asn Ala Thr Leu Leu Leu Pro Asp Val Ile Lys Val Ser Thr	215	220	225
	Arg Ser Ser Glu His Phe Phe Ser Val Phe Leu Asn Ile Asn Glu	230	235	240
25	Thr Phe Lys Leu Met Glu Gln Leu Ala Asn Ile Ala Met Arg Gln	245	250	255
	Leu Leu Asp Asn Glu Gly Phe Glu Gln Asp Arg Ser Leu Pro Lys	260	265	270
30	Leu Lys Arg Lys Ser Pro Lys Lys Val Ser Ala Leu Lys Arg Asp	275	280	285
	Leu Asp Ala Arg Ala Lys Ser Glu Arg Tyr Arg Ala Leu Phe Arg	290	295	300
35	Leu Pro Lys Asp Glu Lys Leu Asp Gly His Thr Asp Cys Thr Leu	305	310	315
	Trp Thr Pro Phe Asn Lys Met His Ile Leu Gly Gln Met Phe Val	320	325	330
40	Ser Thr Asn Tyr Ile Cys Phe Thr Ser Lys Glu Glu Asn Leu Cys	335	340	345
	Ser Leu Ile Ile Pro Leu Arg Glu Val Thr Ile Val Glu Lys Ala	350	355	360
45	Asp Ser Ser Ser Val Leu Pro Ser Pro Leu Ser Ile Ser Thr Arg	365	370	375
	Asn Arg Met Thr Phe Leu Phe Ala Asn Leu Lys Asp Arg Asp Phe	380	385	390
50	Leu Val Gln Arg Ile Ser Asp Phe Leu Gln Gln Thr Thr Ser Lys	395	400	405
55				

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	Ile Tyr Ser Asp	Lys Glu Phe Ala Gly	Ser Tyr Asn Ser Ser Asp	410	415	420
5	Asp Glu Val Tyr	Ser Arg Pro Ser Ser	Leu Val Ser Ser Ser Pro	425	430	435
	Gln Arg Ser Thr	Ser Ser Asp Ala Asp	Gly Glu Arg Gln Phe Asn	440	445	450
10	Leu Asn Gly Asn	Ser Val Pro Thr Ala	Thr Gln Thr Leu Met Thr	455	460	465
	Met Tyr Arg Arg	Arg Ser Pro Glu Glu	Phe Asn Pro Lys Leu Ala	470	475	480
15	Lys Glu Phe Leu	Lys Glu Gln Ala Trp	Lys Ile His Phe Ala Glu	485	490	495
	Tyr Gly Gln Gly	Ile Cys Met Tyr Arg	Thr Glu Lys Thr Arg Glu	500	505	510
20	Leu Val Leu Lys	Gly Ile Pro Glu Ser	Met Arg Gly Glu Leu Trp	515	520	525
	Leu Leu Leu Ser	Gly Ala Ile Asn Glu	Lys Ala Thr His Pro Gly	530	535	540
25	Tyr Tyr Glu Asp	Leu Val Glu Lys Ser	Met Gly Lys Tyr Asn Leu	545	550	555
	Ala Thr Glu Glu	Ile Glu Arg Asp Leu	His Arg Ser Leu Pro Glu	560	565	570
30	His Pro Ala Phe	Gln Asn Glu Met Gly	Ile Ala Ala Leu Arg Arg	575	580	585
	Val Leu Thr Ala	Tyr Ala Phe Arg Asn	Pro Asn Ile Gly Tyr Cys	590	595	600
35	Gln Ala Met Asn	Ile Val Thr Ser Val	Leu Leu Leu Tyr Ala Lys	605	610	615
	Glu Glu Glu Ala	Phe Trp Leu Leu Val	Ala Leu Cys Glu Arg Met	620	625	630
40	Leu Pro Asp Tyr	Tyr Asn Thr Arg Val	Val Gly Ala Leu Val Asp	635	640	645
	Gln Gly Val Phe	Glu Glu Leu Ala Arg	Asp Tyr Val Pro Gln Leu	650	655	660
45	Tyr Asp Cys Met	Gln Asp Leu Gly Val	Ile Ser Thr Ile Ser Leu	665	670	675
	Ser Trp Phe Leu	Thr Leu Phe Leu Ser	Val Met Pro Phe Glu Ser	680	685	690
50	Ala Val Val Val	Val Asp Cys Phe Phe	Tyr Glu Gly Ile Lys Val	695	700	705
55	Ile Phe Gln Leu	Ala Leu Ala Val Leu	Asp Ala Asn Val Asp Lys			

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					710					715					720
5		Leu	Leu	Asn	Cys	Lys	Asp	Asp	Gly	Glu	Ala	Met	Thr	Val	Gly
						725					730				735
		Arg	Tyr	Leu	Asp	Ser	Val	Thr	Asn	Lys	Asp	Ser	Thr	Leu	Pro
						740					745				750
10		Ile	Pro	His	Leu	His	Ser	Leu	Leu	Ser	Asp	Asp	Val	Glu	Tyr
						755					760				765
		Pro	Glu	Val	Asp	Ile	Phe	Arg	Leu	Ile	Arg	Thr	Ser	Tyr	Glu
						770					775				780
15		Phe	Gly	Thr	Ile	Arg	Ala	Asp	Leu	Ile	Glu	Gln	Met	Arg	Lys
						785					790				795
		Gln	Arg	Leu	Lys	Val	Ile	Gln	Thr	Leu	Glu	Asp	Thr	Thr	Lys
						800					805				810
20		Asn	Val	Val	Arg	Thr	Ile	Val	Thr	Glu	Thr	Ser	Phe	Thr	Ile
						815					820				825
		Glu	Leu	Glu	Glu	Leu	Tyr	Ala	Leu	Phe	Lys	Ala	Glu	His	Leu
						830					835				840
25		Ser	Cys	Tyr	Trp	Gly	Gly	Ser	Ser	Asn	Ala	Leu	Asp	Arg	His
						845					850				855
		Pro	Ser	Leu	Pro	Tyr	Leu	Glu	Gln	Tyr	Arg	Ile	Asp	Phe	Glu
						860					865				870
30		Phe	Lys	Gly	Met	Phe	Ala	Leu	Leu	Phe	Pro	Trp	Ala	Cys	Gly
						875					880				885
		His	Ser	Asp	Val	Leu	Ala	Ser	Arg	Leu	Phe	Gln	Leu	Leu	Asp
						890					895				900
35		Asn	Gly	Asp	Ser	Leu	Ile	Asn	Phe	Arg	Glu	Phe	Val	Ser	Gly
						905					910				915
		Ser	Ala	Ala	Cys	His	Gly	Asp	Leu	Thr	Glu	Lys	Leu	Lys	Leu
						920					925				930
40		Tyr	Lys	Met	His	Val	Leu	Pro	Glu	Pro	Ser	Ser	Asp	Gln	Asp
						935					940				945
		Pro	Asp	Ser	Ala	Phe	Glu	Ala	Thr	Gln	Tyr	Phe	Phe	Glu	Asp
						950					955				960
45		Thr	Pro	Glu	Cys	Thr	His	Val	Val	Gly	Leu	Asp	Ser	Arg	Ser
						965					970				975
		Gln	Gly	Ala	Asp	Asp	Gly	Phe	Val	Thr	Val	Ser	Leu	Lys	Pro
						980					985				990
50		Lys	Gly	Lys	Arg	Ala	Asn	Ser	Gln	Glu	Asn	Arg	Asn	Tyr	Leu
						995					1000				1005
55		Leu	Trp	Thr	Pro	Glu	Asn	Lys	Ser	Lys	Ser	Lys	Asn	Ala	Lys
						1010					1015				1020

5	Leu Pro Lys Leu Asn Gln Gly Gln Phe Ile Glu Leu Cys Lys Thr	1025	1030	1035
	Met Tyr Asn Met Phe Ser Glu Asp Pro Asn Glu Gln Glu Leu Tyr	1040	1045	1050
10	His Ala Thr Ala Ala Val Thr Ser Leu Leu Leu Glu Ile Gly Glu	1055	1060	1065
	Val Gly Lys Leu Phe Val Ala Gln Pro Ala Lys Glu Gly Gly Ser	1070	1075	1080
15	Gly Gly Ser Gly Pro Ser Cys His Gln Gly Ile Pro Gly Val Leu	1085	1090	1095
	Phe Pro Lys Lys Gly Pro Gly Gln Pro Tyr Val Val Glu Ser Val	1100	1105	1110
20	Glu Pro Leu Pro Ala Ser Leu Ala Pro Asp Ser Glu Glu His Ser	1115	1120	1125
	Leu Gly Gly Gln Met Glu Asp Ile Lys Leu Glu Asp Ser Ser Pro	1130	1135	1140
25	Arg Asp Asn Gly Ala Cys Ser Ser Met Leu Ile Ser Asp Asp Asp	1145	1150	1155
	Thr Lys Asp Asp Ser Ser Met Ser Ser Tyr Ser Val Leu Ser Ala	1160	1165	1170
	Gly Ser His Glu Glu Asp Lys Leu His Cys Glu Asp Ile Gly Glu	1175	1180	1185
35	Asp Thr Val Leu Val Arg Ser Gly Gln Gly Thr Ala Ala Leu Pro	1190	1195	1200
	Arg Ser Thr Ser Leu Asp Arg Asp Trp Ala Ile Thr Phe Glu Gln	1205	1210	1215
40	Phe Leu Ala Ser Leu Leu Thr Glu Pro Ala Leu Val Lys Tyr Phe	1220	1225	1230
	Asp Lys Pro Val Cys Met Met Ala Arg Ile Thr Ser Ala Lys Asn	1235	1240	1245
45	Ile Arg Met Met Gly Lys Pro Leu Thr Ser Ala Ser Asp Tyr Glu	1250	1255	1260
50	Ile Ser Ala Met Ser Gly	1265		

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Claims

1. An antagonist of a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, for use in a method

of inhibiting the growth of a cancer cell that expresses said Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, said method comprising: contacting said cancer cell with said antagonist.

2. An antagonist for use according to claim 1, wherein the cancer cell is a lung cancer or ovarian cancer cell.
3. An antagonist for use according to claim 1, wherein said inhibition induces death of the cancer cell.
4. An antagonist of a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, for use in a method for the prevention or treatment of a lung tumor or ovarian tumor in a mammal wherein the tumor comprises cells expressing said Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, said method comprising: administering to the mammal an effective amount of said antagonist.
5. An antagonist for use according to claim 4, wherein said TAT polypeptide of SEQ ID NO: 1 07 is expressed by said lung tumor or ovarian tumor cell or by a normal cell in the vicinity of said tumor cell.
6. An antagonist for use according to claim 4, wherein said treatment induces shrinkage of the lung tumor or ovarian tumor.
7. An antagonist for use according to claim 4, wherein said treatment induces death of lung tumor or ovarian tumor cells.
8. An antagonist of a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, for use in a method for the prevention or treatment of a lung or ovary proliferative disorder, said method comprising: administering to a subject in need of such treatment, an effective amount of said antagonist.
9. An antagonist for use according to claim 8, wherein said lung or ovary proliferative disorder is lung cancer or ovarian cancer.
10. An antagonist for use according to claim 1, claim 4, or claim 8, wherein said antagonist is selected from the group consisting of anti-TAT antibodies and fragments thereof, fragments and variants of native TAT polypeptides, peptides, antisense oligonucleotides, and small organic molecules.
11. An antagonist for use according to claim 1, claim 4, or claim 8, wherein said antagonist is further conjugated to a growth inhibitory agent or cytotoxic agent.
12. An antagonist for use according to claim 11 wherein said cytotoxic agent is a toxin.
13. An antibody which binds to a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO: 1 07, for use in a method of inhibiting the growth of a cancer cell that expresses said Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO: 107, said method comprising: contacting said cancer cell with said antibody.
14. An antibody which binds a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, for use in a method for the prevention or treatment of a lung tumor or ovarian tumor in a mammal wherein the tumor comprises cells expressing said Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO: 107, said method comprising: administering to the mammal an effective amount of said antibody.
15. An antibody which binds a Tumor-associated Antigenic Target (TAT) polypeptide of SEQ ID NO:107, for use in a method for the prevention or treatment of a lung or ovary proliferative disorder, said method comprising: administering to a subject in need of such treatment, an effective amount of said antibody.
16. A method of diagnosing the presence of a tumor in a mammal, said method comprising contacting a test sample of tissue cells obtained from said mammal with an antibody that binds to a protein comprising the amino acid sequence of SEQ ID NO:107, and detecting the formation of a complex between said antibody and said protein in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in said mammal.
17. The method of claim 16, wherein said antibody is detectably labeled.
18. The method of claim 16, wherein said test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

19. The method of Claim 18, wherein said tumor is a lung tumor or ovarian tumor.

20. A method of diagnosing the presence of a tumor in a mammal, said method comprising determining the level of expression of a gene encoding a protein comprising the amino acid sequence of SEQ ID NO:107, in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a higher level of expression of said protein in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

21. The method of claim 20, wherein the step of determining the level of expression of a gene encoding said protein comprises:

- a) employing an oligonucleotide in an in situ hybridization or RT-PCR analysis; or
- b) employing an antibody in an immunohistochemistry or Western blot analysis.

22. The method of Claim 20, wherein said tumor is a lung tumor or ovarian tumor.

23. A pharmaceutical composition comprising an effective amount of an antagonist according to any of claims 1 to 12 or an antibody of claims 13 to 15, in admixture with a pharmaceutically acceptable carrier.

24. A kit comprising: (a) a pharmaceutical composition of Claim 23; and (b) a package insert or label indicating a beneficial use for said pharmaceutical composition in the treatment of cancer.

25. The kit of claim 24 wherein said cancer is lung cancer or ovarian cancer.

26. The kit of claim 24 wherein the beneficial use is extension of survival.

27. The kit of claim 24 wherein the beneficial use is progression-free survival.

FIGURE 29

CAGCCCAGCACCTGCGGAGGGAGCGCTGACCAATGGGCTCCCTGGCCTGAATTGGGAGATGCCCAGCCCAACCCCG
 ATAAGTACCTCGAAGGGGCGCAGGTCAGCAGCCCACTGCCCCGATAAAAAGCAAAGAGACCAACAAAACAGAT
 AACACTGAGGCACCTGTAACCAAGATTGAACCTTCTGCCGTCTACTCCACGGCTACACTGATAGATGAGCCAC
 TGAGGTGGATGACCCCTGGAACCTACCCACTCTTCAGGACTCGGGGATCAAGTGGTCAGAGAGAGACACCAAAG
 GGAAGATTCTCTGTTTCTTCCAAGGGATTGGGAGATTGATTTTACTTCTCGGATTTCTCTACTTTTTTCGTGTGC
 TCCCTGGATATTCTTAGTAGCGCCTTCCAGCTGGTTGGAGGAAAAATGGCAGGACAGTTCTTCAGCAACAGCTC
 TATTATGTCCAACCCCTTTGTTGGGGCTGGTGATCGGGGTGCTGGTGACCGTCTTGGTGCAGAGCTCCAGCACCT
 CAACGTCCATCGTTGTGAGCATGGTGTCTCTTCATTGCTCACTGTTCCGGGCTGCCATCCCCATTATCATGGGG
 GCCAACATTGGAACGTCAATCACCAACACTATTGTTGCGCTCATGCAGGTGGGAGATCGGAGTGAGTTCAGAAG
 AGCTTTTGCAGGAGCCACTGTCCATGACTTCTTCAACTGGCTGTCCGTGTTGGTGCTCTTGCCCGTGGAGGTGG
 CCACCCATTACCTCGAGATCATAACCCAGCTTATAGTGGAGAGCTTCCACTTCAAGAATGGAGAAGATGCCCCA
 GATCTTCTGAAAAGTCATCACTAAGCCCTTCAAAAGCTCATTGTCCAGCTGGATAAAAAAGTTATCAGCCAAAT
 TGCAATGAACGATGAAAAAGCGAAAAACAAGAGTCTTGTCAAGATTGGTGCAAAACTTTTACCAACAAGACCC
 AGATTAACGTCACTGTTCCCTCGACTGCTAACTGCACCTCCCCCTCCCTCTGTTGGACGGATGGCATCCAAAAC
 TGGACCATGAAGAATGTGACCTACAAGGAGAACATCGCCAAATGCCAGCATATCTTTGTGAATTTCCACCTCCC
 GGATCTTGCTGTGGGCACCATCTTGCTCATACTCTCCCTGCTGGTCCCTCTGTGGTTGCCTGATCATGATTGTCA
 AGATCCTGGGCTCTGTGCTCAAGGGGCGAGTGCACCTGTCAAGAGACCATCAACACTGATTTCCCTTTT
 CCCTTTGCATGGTTGACTGGCTACCTGGCCATCCTCGTGGGGCAGGCATGACCTTCATCGTACAGAGCAGCTC
 TGTGTTACGTCGGCCTTGACCCCCCTGATTGGAATCGGCGTGATAACCATTGAGAGGGCTTATCCACTCACGC
 TGGGCTCCAACATCGGCACCAACCACCACCGCCATCCTGGCCGCTTAGCCAGCCCTGGCAATGCATTGAGGAGT
 TCACTCCAGATCGCCCTGTGCCACTTTTTCTTCAACATCTCCGGCATCTGCTGTGGTACCCGATCCCGTTAC
 TCGCCTGCCCATCCGCATGGCCAAGGGGCTGGGCAACATCTCTGCCAAGTATCGCTGGTTCCCGCTCTTCTACC
 TGATCATCTTCTTCTTCTGATCCCGCTGACGGTGTGTTGGCCTCTCGCTGGCCGGCTGGCGGGTGCTGGTTGGT
 GTCGGGGTTCCCGCTCGTCTTCATCATCATCCTGGTACTGTGCCTCCGACTCCTGCAGTCTCGCTGCCCACGCGT
 CCTGCCGAAGAACTCCAGAACTGGAACCTTCTGCCGCTGTGGATGCGCTCGCTGAAGCCCTGGGATGCCGTG
 TCTCCAAGTTCACCGGCTGCTTCCAGATGCGCTGCTGCTGCTGCTGCTGCCGCGTGTGCTGCCGCGCTGCTGCTTG
 CTGTGTGGCTGCCCCAAGTGCTGCCGCTGCAGCAAGTGCTGCGAGGACTTGGAGGAGGCGCAGGAGGGGCAGGA
 TGTCCCTGTCAAGGCTCCTGAGACCTTTGATAACATAACCATTAGCAGAGAGGCTCAGGGTGAGGTCCCTGCCT
 CGGACTCAAAGACCGAATGCACGGCCTTGTAGGGGACGCCCCAGATTGTCAGGGATGGGGGGATGGTCCTTGAG
 TTTTGCATGCTCTCCTCCCTCCCACTTCTGCACCCCTTTCACCACCTCGAGGAGATTTGCTCCCCATTAGCGAAT
 GAAATTGATGCAGTCTACCTAACTCGATTCCCTTTGGCTTGGTGGGTAGGCCTGCAGGGCACTTTTATTCCAA
 CCCATGGCCTCCATGACTTTTTTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 107

MAPWPELGDAQPNPDKYLEGAAGQQPTAPDKSKETNKTNDTEAPVTKIELLPSTATLIDEPTEVDDPWNLP
 LQDSGIKWSERDTKGKILCFFQIGRLILLGLYFFVCSLDILSSAFQLVGGKMAGQFFSNSSIMSNPLLGLV
 IGVLTVLVQSSSTSTSIVVSMVSSSLTVRAAPIIMGANIGTSITNTIVALMQVGRSEFRRAFAGATVHDF
 FNWLSVLVLLPVEVATHYLEIITQLIVESFHFKNGEDAPDLLKVITKPF TKLIVQLDKKVISQIAMNDEKAKNK
 SLVKIWCKTFTNKTQINVTVPSTANCTSPSLCWT DGIQNWMTMKNVTYKENIAKQHIFVNFHLPDLAVGTILLI
 LSLVLVLCGLIMIVKILGSLKGVATVIKKTINTDFPFFAWLTGYLAILVGAGMTFIVQSSSVFTSALTPLI
 GIGVITIERAYPLTLGSNIGTTTTAILAALASPGNALRSSQLALCHFFFNISGILLWYPIPFTRLPIRMAKGL
 GNISAKYRWFAVFYLIIFFFLIPLTVFGLSLAGWRVLVGVGVVVFIIILVLCRLQLSRCPRVLPKKLQNWNF
 LPLWMRSLKPWDAVVS KFTGCFQMRCCCCRVCCCRACCLLCGCPKCCRC SKCCEDLEEAQEGQDVPVKAPETFD
 NITISREAQGEVPASDSKTECTAL

Transmembrane domains.

amino acids 96-116, 136-156, 178-198, 219-239, 356-376, 372-392, 406-426,
 445-465, 488-508, 523-543, 547-567, 563-583, 592-612

N-glycosylation sites.

amino acids 36-39, 136-139, 295-298, 308-311, 313-316, 321-324, 335-338,
 340-343, 495-498, 520-523, 667-670

N-myristoylation sites.

amino acids 23-28, 79-84, 126-131, 131-136, 146-151, 150-155, 187-192,
 191-196, 393-398, 423-428, 460-465, 464-469, 519-524, 546-551, 634-639

4Fe-4S ferredoxins, iron-sulfur binding region signature.

amino acids 635-645

Insulin family signature.

amino acids 621-635

Na⁺/Pi-cotransporter.

amino acids 118-549



EUROPEAN SEARCH REPORT

Application Number
EP 08 01 2996

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	EP 0 875 569 A (SMITHKLINE BEECHAM CORP [US]) 4 November 1998 (1998-11-04) * page 10 * * page 13 *	1,2, 10-13, 16-18, 20,21, 23,24, 26,27	INV. C12Q1/68 C07K16/30 G01N33/50
Y	ROSS D T ET AL: "SYSTEMATIC VARIATION IN GENE EXPRESSION PATTERNS IN HUMAN CANCER CELL CEL LINES" NATURE GENETICS, NATURE PUBLISHING GROUP, NEW YORK, US, vol. 24, 1 March 2000 (2000-03-01), pages 227-235, XP002933374 ISSN: 1061-4036 * the whole document *	20-22	
Y	MCDONIELS-SILVERS M L ET AL: "IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES IN HUMAN LUNG ADENOCARCINOMAS AND SQUAMOUS CELL CARCINOMAS" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, vol. 41, no. 680, 1 March 2000 (2000-03-01), page 680, XP001097529 ISSN: 0197-016X * the whole document *	20-22	TECHNICAL FIELDS SEARCHED (IPC) C07K
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 21 October 2008	Examiner Wagner, René
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EPO FORM 1503 03 82 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 08 01 2996

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